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CONTENTS OF VOLUME 66

JULY 1940 NUMBER 1

	PAGE
Staphylococcic Septicemia Robert T Sutherland, M D, Oakland, Calif	1
Oil Aspiration (Lipoid) Pneumonia in Adults A Clinicopathologic Study of Forty-Seven Cases David G Freiman, M D, Hyman Engelberg, M D, and William H Merrit, M D, New York	11
Bronchogenic Carcinoma, with Special Reference to Results with Roentgen Therapy Robert G Bloch, M D, and George Bogardus, M D, Chicago	39
Primary Tumor of Inferior Vena Cava, with Clinical Features Suggestive of Chiari's Disease Phillip Hallock, M D, C J Watson, M D, and Lawrence Berman, M D, Minneapolis	50
Diagnostic Significance of Determinations of Serum Lipase Thomas A Johnson, M D, and H L Bockus, M D, Philadelphia	62
Basal Insulin Requirement in Diabetes Mellitus Helen Martin, M D, D R Drury, M D, and S Strouse, M D, Los Angeles	78
The Electrocardiogram in Insulin Shock Douglas Goldman, M D, Cincinnati	93
Dermatomyositis and Systemic Lupus Erythematosus I A Clinical Report of "Transitional" Cases, with a Consideration of Lead as a Possible Etiologic Factor Harry Keil, M D, New York	109
Effects of Roentgen Therapy on Histologic Picture and on Survival in Cases of Primary Carcinoma of Lung Paul E Steiner, M D, Ph D, Chicago	140
Oscillometric Readings in Cases of Arteriosclerotic Disease of the Lower Extremity Significance and Interpretation Lawrence N Atlas, M D, Cleveland	155
Relation Between Multiple Peripheral Neuropathy and Cirrhosis of the Liver Edgar Wayburn, M D, and Catherine R Guerard, M D, San Francisco	161
Progress in Internal Medicine	
Blood Review of Recent Literature (Concluded) Raphael Isaacs, M D, Cyrus C Sturgis, M D, Frank H Bethell, M D, and S Milton Goldhamer, M D, Ann Arbor, Mich	173
Review of Literature on the Pituitary Body (1938 and 1939) Edward H Rynearson, M D, and Lamont R Schweiger, M D, Rochester, Minn	226
Book Reviews	291

AUGUST 1940 NUMBER 2

	PAGE
Significance of the Albumin-Globulin Ratio of Serum Daniel Melnick, Ph D, Henry Field Jr, M D, and Christopher G Parnall Jr, M D, Ann Arbor, Mich	295
A Practical Method for the Measurement of Glomerular Filtration Rate (Inulin Clearance), with an Evaluation of the Clinical Significance of This Determination Alf S Alving, M D, and Benjamin F Miller, Ch E, M D, Chicago	306
Purpura Haemorrhagica Due to the Arsphenamines Sensitivity in Patients as Influenced by Vitamin C Therapy Ernest H Falconer, M D, Norman N Epstein, M D, and Edith S Mills, M A, San Francisco	319
Dermatomyositis and Systemic Lupus Erythematosus II A Comparative Study of the Essential Clinicopathologic Features Harry Keil, M D, New York	339

Arteritis of the Temporal Vessels	Report of a Case	James M Bowers, M D, Seattle	384
Body Build and Hypertension		S C Robinson, M D, and Marshall Brucer, S B, Chicago	393
Diagnosis and Treatment of Gonorrheal Septicemia and Gonorrheal Endocarditis		John Staige Davis Jr, M D, New York	418
Bacterial Endocarditis and Syphilis of the Aortic Valve		David H Rosenberg, M D, Chicago	441
Survey of Diabetes	Statistical Data and Control Comparisons with Various Insulins	Bertnard Smith, M D, and William H Grishaw M D, Los Angeles	465
Progress in Internal Medicine			
	Infectious Diseases	A Review of Significant Publications in 1939-1940 Hobart A Reimann, M D, Philadelphia	478
News and Comment			526
Book Reviews			527

SEPTEMBER 1940 NUMBER 3

SEPTEMBER 1940 NUMBER 3		PAGE
Spontaneous Hypoglycemia Due to Atrophy of the Adrenal Glands	Report of a Case Joseph G Rushton, M D , Richard W Cragg, M D , and Leonard K Stalker, M D , Rochester, Minn	531
Hypertension (Goldblatt) and Unilateral Malignant Nephrosclerosis	Otto Saphir, M D , and Joseph Ballinger, M D , Chicago	541
Pulmonary Infection and Necrosis in Diabetes Mellitus	Report of a Case of Dissecting Necrotic Pneumonia Complicating Pancreatic Lithiasis Sylvan E Moolten, M D , New York	561
Structural Changes in the Arterioles of the Myocardium in Diffuse Arteriolar Disease with Hypertension Group 4	Howard M Odel, M D , Rochester, Minn	579
Fatty Degeneration of the Heart Causing Myocardial Insufficiency	Report of a Case Curtis F Garvin, M D , Cleveland	603
Diabetes Insipidus Associated with Diabetes Mellitus	Metabolic Studies and Report of a Case John H Talbott, M D , Frederick S Coombs, M D , W V Consolazio, B S , and L J Pecora, B S , Boston	607
Arterial Blood Pressure in Cases of Auricular Fibrillation, Measured Directly	W C Buchbinder, M D , and H Sugarman, M D , Chicago	625
Renal Involvement in Disseminated Lupus Erythematosus	J Minott Stickney, M D , and Norman M Keith, M D , Rochester, Minn	643
Measurement of Vitamin A Status of Young Adults by the Dark Adaptation Technic	Evelyn Lyman Blanchard, Ph D , Davis, Calif , and Harold A Harper, Sc B , Los Angeles	661
Protamine Zinc Insulin	A Clinical Study, Report of a Group of Diabetic Patients in Whose Cases Glycosuria Was Disregarded for One Year Edward Tolstoi, M D , and Frederick C Weber Jr, M D , New York	670
Evaluation of Vitamin B Therapy for Diabetes	Louis B Owens, M D , Samuel S Rockwern, M D , and Edna G Brown, B S , Cincinnati	679
Pancreatic Secretion in Man After Stimulation with Secretin and Acetyl-beta-methylcholine Chloride	A Comparative Study Mandred W Comfort, M D , and Arnold E Osterberg, Ph D , Rochester, Minn	688
Progress in Internal Medicine		
	Vascular Diseases A Review of Some of the Recent Literature, with a Critical Review of the Surgical Treatment George W Scupham, M D , Geza de Takats, M D , Theodore R Van Dellen, M D , and William C Beck, M D , Chicago	707
Book Reviews		777
News and Comment		784

OCTOBER 1940 NUMBER 4

	PAGE
Observations on Induced Thiamine (Vitamin B ₁) Deficiency in Man Ray D Williams, M D , Harold L Mason, Ph D , Russell M Wilder, M D, Ph D, and Benjamin F Smith, M D, Rochester, Minn	785
Pain in the Shoulder as a Sequel to Myocardial Infarction A Carlton Ernstene, M D, and Jack Kinell, M D, Cleveland	800
Interauricular Septal Defect W S Tinney Jr, M D, Lancaster, Pa	807
Relative Significance of Concentration of Inorganic Sulfate in the Serum and of Its Renal Clearance, with Special Reference to Diffuse Arteriolar Disease with Hypertension Arnoldus Goudsmit Jr, M D, and Norman M Keith, M D, Rochester, Minn	816
Pancreatic Function in a Case of Nontropical Sprue Alice Childs, M D, and George F Dick, M D, Chicago	833
Normal Blood Pressure Alan E Treloar, Ph D, Minneapolis	848
Necrobiosis Lipoidica Diabeticorum Alice G Hildebrand, M D, Hamilton Montgomery, M D, and Edward H Ryneerson, M D, Rochester, Minn	851
Banti Syndrome (Fibrocongestive Splenomegaly) Definition, Classification and Pathogenesis Paolo Ravenna, M D, Chicago	879
Progress in Internal Medicine	
Gastroenterology Review of Literature from July 1939 to July 1940 Chester M Jones, M D, Boston	893
Correspondence	
Wire-Loop Lesions Paul Klemperer, M D, New York	1005
Book Reviews	1006

NOVEMBER 1940 NUMBER 5

	PAGE
Diabetes Mellitus and Syphilis A Study of Two Hundred and Fifty-Eight Cases L Tillman McDaniel, M D, Boston, Herbert H Marks, B A, New York, and Elliott P Joslin, M D, Boston	1011
Electrolyte Balance During Treatment, Crises and Severe Infection in Cases of Addison's Disease Action of Adrenal Cortical Extracts James A Greene, M D, and George W Johnston, M S, Iowa City	1052
Anatomic Foundation of Anacidity A Gastroscopic Study Rudolf Schindler, M D, and Paul B Nutter, M D, Chicago, Horace Ensign Groom, M D, Akron, Ohio, and Walter Lincoln Palmer, M D, Chicago	1060
Influence of Thiamine on Blood Sugar Levels in Diabetic Patients Robert E Kaufman, M D, New York	1079
Relation of Fatty Acids and Bile Salts to the Formation of Gallstones Ralph E Dolkart, M D, Boston, and Marie Lorenz, B A, K K Jones, Ph D, and Clarence F G Brown, M D, Chicago	1087
Syndrome of Subnormal Circulation in Ambulatory Patients Isaac Starr, M D, and Leon Jonas, M D, Philadelphia	1095
Progress in Internal Medicine	
Syphilis Review of the Recent Literature Charles F Mohr, M D, Paul Padget, M D, and Joseph Earle Moore, M D, Baltimore	1112
Book Reviews	1188

DECEMBER 1940 NUMBER 6

	PAGE
Experiments on the Properties of the Extrinsic Factor and on the Reaction of Castle P Formijne, M D, Amsterdam, Netherlands	1191
Transitory Infiltration of the Lung with Eosinophilia Löffler's Syndrome R Freund, M D, and S Samuelson, M D, Jerusalem, Palestine	1215
Subacute Cor Pulmonale David G Mason, M D, San Francisco	1221

Studies of the Blood in Congestive Heart Failure, with Particular Reference to Reticulocytosis, Erythrocyte Fragility, Bilirubinemia, Urobilinogen Excretion and Changes in Blood Volume	John V Waller, M D , Herrman L Blumgart, M D , and Marie C Volk, A B , Boston	1230
Comparison of Sulfathiazole and Sulfapyridine in Treatment of Pneumococcic Pneumonia	Curtis F Garvin, M D , Cleveland	1246
Acacia in the Treatment of the Nephrotic Syndrome	Arnoldus Goudsmit Jr, M D , Philadelphia, and Melvin W Binger, M D , Rochester, Minn	1252
Cerebral Abscess (Paradoxical) Accompanying Congenital Heart Disease Report of Two Cases	I S Wechsler, M D , and Abraham Kaplan, M D , New York	1282
Pneumococcic Pneumonia Analysis of the Records of 1,469 Patients Treated in the Los Angeles County Hospital from 1934 Through 1938		
I Character of Pneumonia Caused by the Various Types of Pneumococci, Complications, Outcome of Pneumonia in the Presence of Certain Variations in the Patient and in the Course of the Disease	Frederick J Moore, B A , Roy E Thomas, M D , Maxwell Kistler, B A , Robert M Ireland, B A , and Victor E Hallstone, B A , Los Angeles	1290
II Outcome and Character of Pneumonia in the Presence of Associated or Concomitant Conditions	Frederick J Moore, B A , Burrell O Raulston, M D , Roy E Thomas, M D , Joseph F Maguire, and Gerald K Ridge, Los Angeles	1317
Multiple Primary Malignant Lesions of the Large Bowel	Lamont R Schweiger, M D , and J Arnold Barger, M D , Rochester, Minn	1331
Progress in Internal Medicine		
Review of Neuropsychiatry for 1940	Stanley Cobb, M D , Boston	1341
News and Comment		1355
Book Reviews		1356
General Index		1361

STAPHYLOCOCCIC SEPTICEMIA

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The diagnosis of staphylococcic septicemia brings to many minds a well grounded fear as well as a feeling of unfortunate hopelessness. This hopelessness is an unhealthy condition, often leading either to procrastination with the loss of life-saving time or to the waste of valuable therapeutic agents because of inadequate dosage. The fear, however, together with a healthy stimulation of ingenuity, is undoubtedly praiseworthy. It should not only produce an increase in early recoveries together with a decrease in cases of chronic osteomyelitis, but it should also encourage scientific workers to renewed efforts in discovering more efficient and more specific means of treatment. When this is done there will be a reduction in the exceedingly high mortality.

MORTALITY

The mortality, as observed in statistics of staphylococcic septicemia, varies greatly. In 1936 MacNeal and Friesbee¹ reported a death rate of 75 per cent for a series of 100 patients of all ages treated by bacteriophage. Rosenow and Brown² reported a rate of 66 per cent for a series of patients seen between 1934 and 1936. Mendell,³ in reviewing the reports on a series of 35 patients having the disease between 1929 and 1937, found 29 deaths, or 83 per cent. In 1939 Stookey and Scarpellino⁴ gathered reports on a series of 177 patients treated by various means, with a death rate of 91.4 per cent, while of 17 patients whom they treated with staphylococcus antitoxin they lost 9, or 53 per cent. This last figure corresponds closely with the figures reported by

From the Cowell Memorial Hospital, University of California, Berkeley

1 MacNeal, W. J., and Friesbee, F. C. *Am J M Sc* **191** 179 (Jan.) 1936

2 Rosenow, E. C., and Brown, A. E. *Proc Staff Meet, Mayo Clin* **13** 89 (Feb. 9) 1938

3 Mendell, T. H. Staphylococcic Septicemia. Review of Thirty-Five Cases with Six Recoveries, Twenty-Nine Deaths and Sixteen Autopsies, *Arch Int Med* **63** 1068 (June) 1939

4 Stookey, P. F., and Scarpellino, L. A. *South M J* **32** 173 (Feb.) 1939

Dolman,⁵ one of the pioneers of treatment with antitoxin. The death rate which he reported as early as 1934 was reduced to 55 per cent by the use of antitoxin.

Encouraging results from the use of antitoxin and immune blood have prompted this report on patients with staphylococcic septicemia who were encountered by the staff at the students' health service of the University of California. The series extends over a period of thirty years, from 1909 to 1938 inclusive. Only those patients are included who manifested initial carbuncles, furuncles or blisters, together with positive blood cultures and other evidence of grave infection. There was a total of 7 such patients. Of these, 2, or 28.6 per cent, died. The only patient treated prior to the use of antitoxin died. Of the 6 treated since 1937 with large doses of antitoxin, only a single patient, or 16.7 per cent, died.

Data on Seven Patients with Staphylococcic Septicemia

Case	Age	Sex	Primary Focus	Day of First Positive Blood Culture	Specific Treatment			Days in Hospital	Result
					Antitoxin, Units	Immune Blood, Cc	Toxoid, Cc		
1926	20	♂	Furuncle	2	None			4	Death
1937	20	♂	Blister	3	460,000			24	Recovery
1938	18	♀	Furuncle	1	630,000	480		53	Recovery
1938	18	♀	Furuncle	7	340,000	100		19	Recovery
1938	21	♂	Furuncle	5	340,000		1.9	40	Recovery
1938	22	♂	Furuncle	12	1,030,000			36	Death
1938	23	♂	Blister	5	740,000	535	1.9	92	Recovery

INCIDENCE

Although the death rate among patients with an infection of the blood stream with the staphylococcus has been so high, it is interesting and encouraging that the occurrence of the disease is comparatively infrequent when compared with the great number of patients with superficial infections, such as carbuncles and boils. This series of 7 patients with septicemia was observed during the thirty year period among a total of 11,568 patients with carbuncles, boils and blisters, or at a rate of 6 patients with septicemia per 10,000 of the total number having superficial infections. Although the percentage of superficial infections was much lower in women than in men, the percentage with staphylococcemia was equal in the sexes. All of the patients in this series were within the limits of 18 to 23 years of age. There were 2 girls and 5 boys. Other interesting facts are found in the accompanying table.

⁵ Dolman, C. E. (a) *Canad. M. A. J.* **30**:601 (June) 1934, (b) **31**:1 (July) 1934, (c) **31**:130 (Aug.) 1934.

CLINICAL COURSE AND COMPLICATIONS

All of the patients had irregular septic temperatures, the highest point varying from 39 C (102.2 F) to 42.5 C (108.5 F). Leukocytosis was present in all the patients, the white cell count varying from 10,700 to 41,000 in most of the patients. Three of the 7 patients, or 43 per cent, had bilateral bronchopneumonia. One of these patients died. A pure culture of *Staphylococcus aureus* was recovered from the urine of 2 patients. One of these patients died, and autopsy revealed a cloudy swelling of the kidneys. A third patient showed a transient hemorrhagic nephritis, which completely cleared. Osteomyelitis was found in 2 patients. Roentgen examination revealed it in 1 patient who recovered, and in the other it was proved at autopsy. Multiple superficial pustules and deep abscesses occurred in 1 patient who died. Pure *Staph. aureus* was recovered from an infection of the umbilicus in 1 patient.

TREATMENT

The treatment consisted of surgical, supportive and specific measures. Surgical treatment with adequate drainage of the primary infecting focus was instituted. The only patient to die among those receiving antitoxin showed multiple abscesses. These were located over the right sacroiliac and the left sternoclavicular joints, in the superficial tissues of the left infraclavicular area and in the superficial and deep tissues of the left side of the neck. All abscesses were freely drained. The supportive measures consisted of careful nursing, of a well balanced and adequate caloric intake and of care of the water balance, with intravenous injection of fluids and transfusions of whole blood when indicated. For specific treatment, there were used for all patients since 1937 early and large doses of staphylococcus antitoxin⁶. The total individual dose ranged from 340,000 to 1,080,000 units and was given intramuscularly. In 3 patients immune blood was injected intramuscularly. The only patient of the group to die after being treated with antitoxin did not receive any immune blood. The immune blood was whole blood containing bacterial antibodies from donors who had been immunized by injections of undenatured staphylococcus antigens, as recommended by Dr. A. P. Krueger, professor of bacteriology at the University of California. Two patients received 19 cc of toxoid⁶ during their convalescence.

6 All the antitoxin and toxoid used for these patients was from the Lederle Laboratories.

There are two outstanding theories of immunity to the staphylococcus. According to one theory, immunity is due to the amount of antitoxin in the tissues. Burnet⁷ demonstrated in 1929 that certain strains of the staphylococcus produce a virulent exotoxin. Branch⁸ summarized the five proved effects of exotoxin on the various tissues of the body. These are as follows: hemolysis of the erythrocytes due to hemolysin, destruction of the leukocytes by leukocidin, necrosis of tissues, coagulation of the blood plasma by the coagulase and, finally, death due to the lethal element. If treatment is to be effective, the first theory is that there must be sufficient antitoxin present to prevent tissue change by these toxic elements. As the natural antitoxin content varies greatly and is frequently absent, treatment to be effective must early supply sufficiently large quantities of antitoxin. Advocates of the second theory maintain that immunity is due to the content of bactericidal and phagocytic elements in the tissues and in the cells. As these elements are not present in antitoxin they must be supplied by other agents, such as immune blood, or by chemotherapeutic substances, possibly of the nature of sulfapyridine. As this agent was not available during the treatment of the patients in this series, immune blood was used in the treatment of 3 patients.

REPORT OF CASES

CASE 1—A 20 year old white youth entered the hospital complaining of a boil in one nostril and an elevated temperature. A blood culture was positive for *Staph aureus* on the second day. Symptoms of meningitis appeared, but on examination it was observed that the spinal fluid was normal. The temperature rose steadily from 38.5 C (101.3 F) to 41.4 C (106.5 F). The patient died on the fourth day. Treatment was symptomatic.

CASE 2—A white youth aged 20 entered the hospital complaining of pain in the right hip which excluded all motion of the leg. Two weeks previously he sustained blisters of the feet, which became infected. Three days before entry he had chills, fever, sweats and vomiting. Physical examination revealed (1) tenderness over the right iliac crest and to the right of the umbilicus, pain in both instances being referred to the right sacroiliac region, but no tenderness over the joint, (2) old blisters on the soles of both feet, and (3) a temperature of 38.8 C (101.8 F). Laboratory reports showed that the urine, which on the patient's entry had a white blood cell count of 1 to 3 and a red blood cell count of 50 to 80, was entirely normal in twelve days. Examination of the blood showed that during the acute sickness the white cell count ranged from 8,050 to 26,200. The count of the nonfilamented leukocytes, which was as high as 63 when the infection was severest, varied from 43 to 23 for a week after antitoxin was dis-

7 Burnet, F. M. *J. Path. & Bact.* **32**: 717 (Oct.) 1929.

8 Branch, A. *Canad. M. A. J.* **39**: 391 (Oct.) 1938.

continued and the patient well on the way to recovery. Blood cultures were positive for *Staph aureus* on the first, second, third and fifth day but were negative thereafter, on seven examinations. Roentgenograms of the right sacroiliac joint taken two weeks after entry showed a pathologic condition of the right sacroiliac joint, with considerable osteomyelitis of the adjacent bone. Beginning two days after admission, when the first positive blood culture was reported, the patient received a total of 460,000 units of staphylococcus antitoxin in eight days. The temperature varied from 37.5 C (99.6 F) to 40 C (104 F). The patient was dismissed to his home in twenty-five days. Four days later a thrombophlebitis appeared in the left leg, which caused some inconvenience for a few weeks. Roentgenograms of the right sacroiliac joint taken nine months after onset showed complete restoration of the joint with increased calcification of the surrounding bony tissues. Recovery was complete.

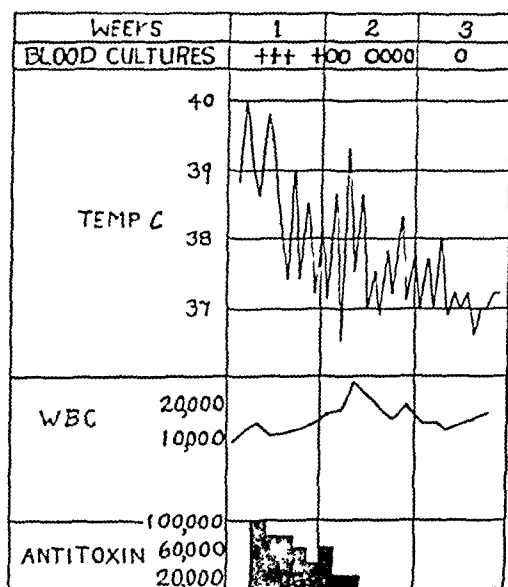


Chart 1—Data on case 2

CASE 3—A white youth aged 22 entered the hospital complaining of severe pain in the right sacroiliac region and of an elevated temperature and malaise of four days' duration. He gave a history of having had a boil on his right wrist twelve days before entry. Physical examination revealed only a small draining boil on the right wrist, tenderness in the right sacroiliac region and a temperature of 37.5 C (99.5 F). Laboratory reports indicated that the urine, which was normal for two weeks, began to show a trace of albumin and occasional red and white blood cells, and by the nineteenth day the urine showed a pure culture of *Staph aureus*. Examination of the blood revealed that the red cell count ranged from 3,500,000 to 3,900,000 and the white cell count from 10,000 to 34,200. Blood cultures were negative from the time of the patient's entry until the eleventh day, when *Staph aureus* was recovered. They again became negative after the administration of 400,000 units of antitoxin, but after further progress of the disease they became positive until the patient's death. Roentgenograms showed no abnormality of the sacroiliac joint, of the lumbar spine or of the sternoclavicular joint. Films taken two days before death showed a number of small scattered abscesses of the lungs and a retropharyngeal abscess.

Because of the history of a furuncle, sacroiliac pains and elevated temperature, although blood cultures were repeatedly negative until the eleventh day, the administration of antitoxin was started on the eighth day. On the eleventh day, the day on which the first positive blood culture was obtained, an abscess of the right sacroiliac joint was drained. On the fourteenth day, when the patient received the last dose of the first 400,000 units of antitoxin, the white cell count was 22,600, with 42 filamented and 42 nonfilamented leukocytes. On the next day the white cell count was 24,750, with 72 filamented and 16 nonfilamented leukocytes. This shift toward the right, together with a general improvement and four negative blood cultures, was deceiving. On the seventeenth day an inflammation began in the region of the left sternoclavicular joint and spread to the chest wall, to the neck and to the retropharyngeal space. For multiple abscesses which formed, numerous incisions were made. Although an additional 680,000 units of antitoxin was given, making a total of 1,080,000 units, the patient died on the

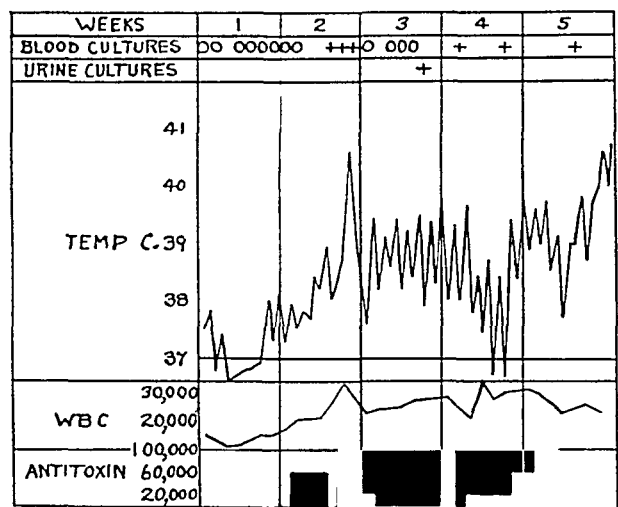


Chart 2—Data on case 3

thirty-fifth day. The diagnosis made at autopsy was multiple staphylococcic abscesses of the neck, the retroesophagus, the retropharynx, the left sternoclavicular and the right sacroiliac joint, multiple abscesses of the skin, bilateral bronchopneumonia with multiple septic infarcts, bilateral acute adhesive pleuritis, acute myocardial degeneration, acute hepatitis, acute splenitis, and cloudy swelling of the kidneys.

CASE 4 (permission of Dr. Ruby L. Cunningham).—A white girl aged 18 entered the hospital complaining of a furuncle over the right eye of four days' duration, accompanied by fever. Physical examination revealed only a large furuncle with edema and redness of the forehead above the right eye, marked edema of the right eyelids and a temperature of 39.8 C (103.6 F). Laboratory reports showed the urine to be normal at all times. Examination of the blood showed a white cell count ranging between 8,000 and 21,000 during the illness. Blood cultures were positive for *Staph. aureus* on the second and fourth days. The administration of antitoxin and immune blood, which was started on the

second day, was continued until the twenty-ninth day because of bilateral broncho-pneumonia manifesting itself on the ninth day. No other complications occurred. The temperature varied from 36.6 C (98 F) to 40.6 C (105.2 F). A total of 630,000 units of antitoxin and 480 cc of immune blood was given. Recovery was complete.

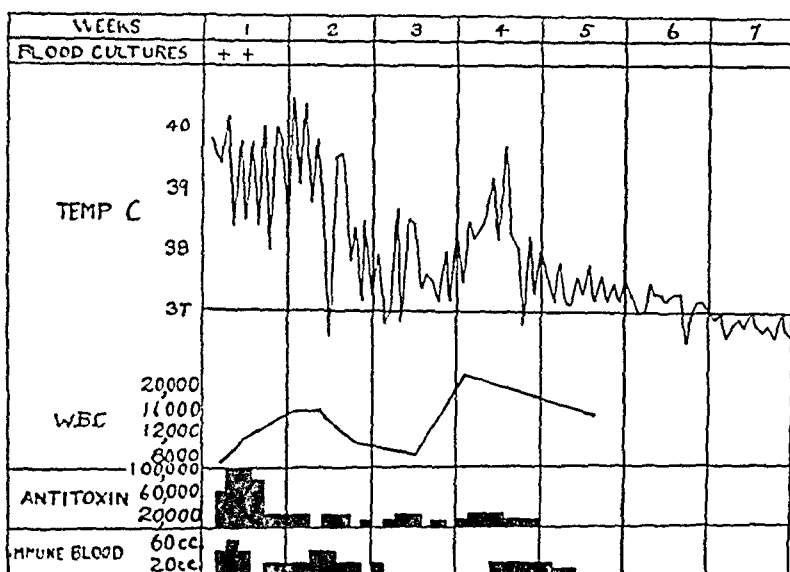


Chart 3—Data on case 4

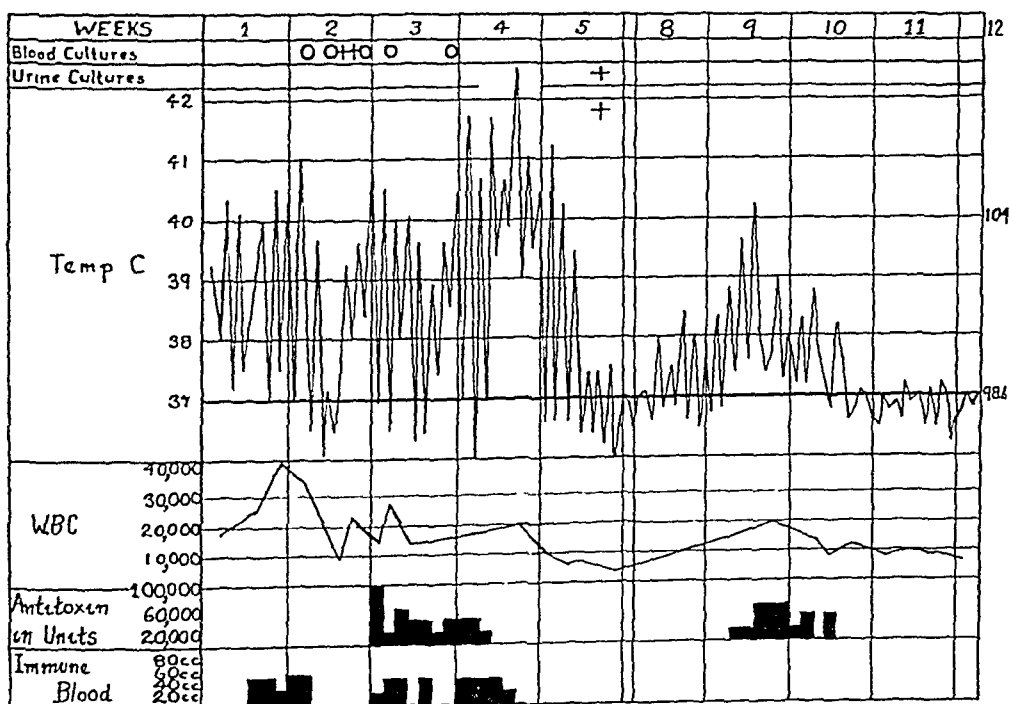


Chart 4—Data on case 5

CASE 5—A white youth aged 23 entered the hospital complaining of severe sore throat, anorexia, nausea, chills and fever. Three weeks before he thought that an insect had bitten his left ankle. The extreme itching caused him to scratch the area, with two pustules resulting. The pustules healed, but two days before his entry to the hospital an inflammation started at the umbilicus. Physical

examination gave negative results except for an elevated temperature, a reddened pharynx, slight cervical lymphadenitis, inflammation of the umbilicus and two small healed scars on the inner aspect of the left ankle. Laboratory examination of the urine revealed that it remained normal until the thirty-fifth and thirty-sixth days, when pure cultures of *Staph aureus* were obtained. Examination of the blood showed that the white cell count varied between 9,350 and 41,500 during the first and severest episode, it then dropped as low as 3,500 between episodes and varied again between 10,200 and 19,600 during the second episode. Blood cultures were positive for *Staph aureus* on the twelfth and thirteenth days. Umbilical cultures were positive for *Staph aureus* on the tenth day. Roentgenograms of the chest taken on the thirty-second day showed bilateral bronchopneumonia.

This patient was the sickest of any of the patients who recovered. The administration of antitoxin, which was started on the fourteenth day, was continued until a total of 420,000 units had been given by the twenty-third day. During the same time 535 cc of immune blood was given. The temperature returned to normal by the thirty-fourth day and remained so until the fiftieth, when the

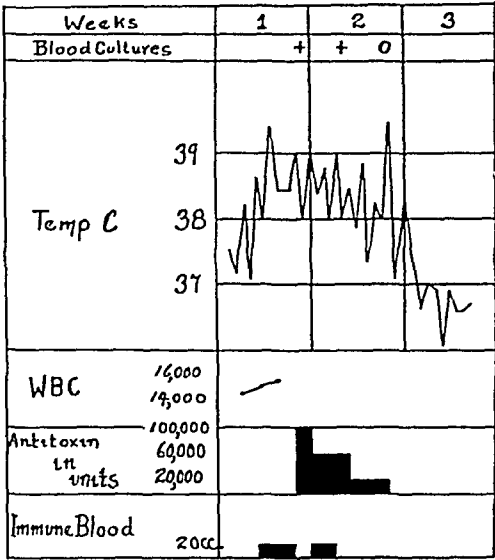


Chart 5—Data on case 6

patient was allowed to sit in a chair for fifteen minutes. The second episode began here with a rising temperature, which by the fifty-seventh day reached 39.6 C (103.4 F). The administration of antitoxin was again started, and during the next eight days an additional 320,000 units was given. The temperature quickly returned to normal. A total of 740,000 units of antitoxin and 535 cc of immune blood was given. The patient left the hospital on the ninety-second day to convalesce at his home in southern California. Recent reports have shown a steady return to health without complications.

CASE 6 (permission of Dr. Ruby Cunningham) —A white girl aged 18 entered the hospital complaining of a furuncle of the forehead of four days' duration and a temperature of 38.1 C (100.6 F). It was known that she had diabetes mellitus. Physical examination revealed nothing abnormal except a large furuncle of the right side of the forehead, a swelling of the eyelids severe enough to close both eyes and an elevated temperature. Laboratory reports on the urine showed dextrose 4 plus, and acetone, 2 plus. These conditions were quickly brought to normal with proper diet and insulin. The white blood cell count ranged between

11,700 and 24,100 Blood cultures were positive for *Staph aureus* on the sixth and ninth days Between the fourth and ninth days, a total of 100 cc of immune blood was given Between the time that the blood culture was reported positive on the sixth day to the thirteenth day, a total of 340,000 units of antitoxin was given The temperature remained normal after the fifteenth day, and the patient was dismissed on the twenty-ninth day Recovery was complete

CASE 7—A white youth aged 21 gave a history of sleepiness and dizziness for three weeks, which with other signs led to a diagnosis of encephalitis During a dizzy spell he struck his right cheek against the wall Soon after, a furuncle developed on the same cheek, attended by a rise in temperature, so he entered the hospital Physical examination showed a discharging furuncle with surrounding redness and edema of the right cheek The tonsils were chronically infected There was some weakness of the left triceps muscle Otherwise the examination gave negative results Laboratory examination showed the urine to be normal, except for an occasional white blood cell The examination of the blood showed that the white cell count ranged between 4,100 and 10,700 Blood cultures were positive on the fourth and seventh days for *Staph aureus* The patient's temperature ranged from 37 C (98.6 F) to 39 C (102.2 F) Between the seventh and four-

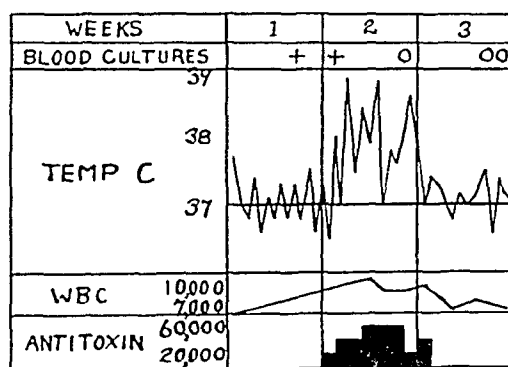


Chart 6—Data on case 7

teenth days 340,000 units of antitoxin was administered The boy was dismissed from the hospital on the thirty-ninth day with a low grade fever A recent letter reported that his strength had returned to normal

SUMMARY

The case histories of 7 students between 18 and 23 years of age who had staphylococcic septicemia are reported These 7 patients were the total number to have an infection of the blood stream among a total of 11,568 patients with carbuncles, furuncles and blisters during a period of thirty years Two of the 7 patients died, or 28.6 per cent Of the 6 patients treated with antitoxin, 3 of whom received immune blood, only 1 died, or 16.7 per cent As to complications, of 3 who had bilateral bronchopneumonia, 1 died, of 3 who showed signs of genitourinary involvement, 1 died, and of 2 with osteomyelitis, 1 died The doses of antitoxin varied from 340,000 to 1,080,000 units Three of the patients who recovered received from 100 to 535 cc of immune blood, and 2 received 19 cc of toxoid during convalescence

CONCLUSIONS

1 The treatment of staphylococcic septicemia should not be considered hopeless, since by early active treatment the mortality can be reduced

2 Patients having active or recently healed carbuncles, furuncles or blisters, with either prolonged, mounting or septic temperatures for which no cause can be found, patients with symptoms and signs of a beginning osteomyelitis and patients with staphylococci in the blood should immediately have heroic treatment

3 At present there is no standard as to what constitutes such treatment

4 Experience suggests that in addition to supportive and surgical care, early treatment with large doses of antitoxin in a total dosage varying from 300,000 to 1,000,000 or more units,⁹ together with some bactericidal element such as immune blood, gives encouraging results

9 Since submitting this article, I have been administering antitoxin intravenously in daily doses of 100,000 units and decreasing the amount only as improvement in signs and symptoms justifies it

OIL ASPIRATION (LIPOID) PNEUMONIA IN ADULTS

A CLINICOPATHOLOGIC STUDY OF FORTY-SEVEN CASES

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In recent years a condition commonly known as lipoid pneumonia but more appropriately termed oil aspiration pneumonia¹ or simply oil pneumonia² has been brought to the notice of the medical profession with increasing frequency. The outstanding features of the disease have been described at length by many writers, and attention has been repeatedly drawn to the danger of using oily medication for infants and, to a lesser degree, for adults. Despite this, it is apparent from the errors in clinical diagnosis detected at postmortem examination that many physicians are still not aware of the relative frequency of this condition, particularly in adults.

Laughlen³ in 1925 reported 5 instances of oil pneumonia in human beings, 1 of whom was a man aged 37. The condition had been produced experimentally, however, at an earlier date. Gueysse-Pellissier⁴ in 1920 observed that intratracheal instillation of olive oil was capable of producing a mononuclear and polymorphonuclear response in the

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1 (a) Ikeda, K. Oil Aspiration Pneumonia (Lipoid Pneumonia), *Am J Clin Path* **5** 89 (March) 1935, (b) Oil Aspiration Pneumonia (Lipoid Pneumonia), *Am J Dis Child* **49** 985 (April) 1935 (c) Houck, G. M. Pulmonary Oil Tumors, Granulomata Caused by Intratracheal Instillation of Liquid Petrolatum (Lipoid or Oil Aspiration Pneumonia), in *Medical Papers Dedicated to Henry Asbury Christian, in Honor of His Sixtieth Birthday*, Baltimore, Waverly Press, 1936, pp 463-478 (d) Fetterman, G. H. Oil Aspiration Pneumonia, *J Lab & Clin Med* **22** 619 (March) 1937

2 (a) Hayes, J. N., and Gardner, L. V. Oil Pneumonia, Experimental and Clinical, *Tr Am Clin & Climat A* **50** 192, 1934 (b) Ritchie, G. Oil Pneumonia, *Wisconsin M J* **35** 286 (April) 1936

3 Laughlen, G. F. Studies on Pneumonia Following Naso-Pharyngeal Injections of Oil, *Am J Path* **1** 407 (July) 1925

4 Gueysse-Pellissier, A. Recherches sur l'absorption de l'huile dans le poumon, *Compt rend Soc de biol* **83** 809, 1920

• lungs of animals Coiper and Freed⁵ in 1922 demonstrated that liquid petrolatum so introduced into rabbits induced proliferative bronchopneumonia. Similar results were obtained with olive oil, while chaulmoogra oil produced a violent pulmonary inflammation. In 1927, Pinkerton⁶ reported several cases of oil aspiration pneumonia in infants and found that a number of fats and oils were responsible agents in patients of this age group, at this time he also made a study of the staining reactions of the various oils in the lung. In 1928 the same author⁷ published the results of a thorough experimental study of pulmonary reactions to animal, vegetable and mineral oils. Using rabbits, he demonstrated that animal oils, such as cod liver oil, milk fat and lard oil, produced fibrosis and giant cell formation in the lung together with necrosis and edema depending on the amount of free fatty acid present in the oil or liberated in the lung by hydrolysis. Vegetable oils, such as the iodized sesame and poppyseed oils used in bronchography, and olive oil⁸ produced practically no reaction. A notable exception to this was chaulmoogra oil. Liquid petrolatum induced a marked macrophagic response together with giant cell formation and some fibrosis by the end of the second or the third month. The amount of fibrosis in the experimental animals, however, was in no way comparable to that which he had observed in 2 infants in whom liquid petrolatum had entered the lungs. This work has since been widely corroborated and enlarged on by others, among them Ikeda^{1a} and Paterson⁹.

Ikeda¹⁰ summarized the literature up to April 1936 and listed 106 cases, 39 of the patients were adults. In a thorough review of the literature through March 1939 we have been able to bring the total number of adult patients to 58, including 2 girls aged respectively 14 and 17 years. In 42 cases the diagnosis was either established or confirmed at autopsy.

5 Coiper, H. J., and Freed, H. The Intratracheal Injection of Oils for Diagnostic and Therapeutic Purposes, *J. A. M. A.* **79** 1739 (Nov. 18) 1922.

6 Pinkerton, H. Oils and Fats. Their Entrance into and Fate in Lungs of Infants and Children, *Am. J. Dis. Child.* **33** 259 (Feb.) 1927.

7 Pinkerton, H. Reaction to Oils and Fats in the Lungs. *Arch. Path.* **5** 380 (March) 1928.

8 Considerable discrepancy in the results obtained with olive oil is evident in early reports. Since commercial olive oil may contain a highly variable amount of free fatty acid, it seems likely that the differences in experimental results are due for the most part to this variation and that the nonirritating character of the oil used by Pinkerton in his experiments was due to its low fatty acid content.

9 Paterson, J. L. H. Pneumonia Following Aspiration of Oily Substances - Lipoid Cell Pneumonia, *J. Path. & Bact.* **46** 151 (Jan.) 1938.

10 Ikeda, K. Lipoid Pneumonia of Adult Type (Paraffinoma of Lung), *Arch. Path.* **23** 470 (April) 1937.

We are reporting on a group of 47 additional adult patients, ranging in age from 20 to 82 years. Of these, 41 were chosen from about 3,500 consecutive autopsies performed at the Montefiore Hospital during the past ten years. Only those cases were considered in which the microscopic observations were characteristic and the gross pictures at least reasonably compatible with the diagnoses so far as they were described. Since macrophages filled with lipoid material may be seen in the lesions of pulmonary tuberculosis (especially tuberculous pneumonia) or in the vicinity of large infarcts, cases in which such conditions were present were selected only if the pathologic picture and the staining reactions¹¹ offered incontrovertible evidence of the nature of the etiologic agent and if at least one lipoid area was in a lobe other than that involved by the tuberculous or the hemorrhagic process. Finally, all cases were omitted in which only a few foam cells or oil droplets were found, since the condition in these was felt to be due in all probability to terminal aspiration.

Six additional cases in which the clinical and roentgen findings are characteristic of this disease and in which the patients are in the hospital wards at the time of writing have also been included. Some of these cases were discovered by routine roentgen examination of patients with dysphagia in the neurologic service. A seventh patient, originally in this group, died during this study, and the diagnosis was confirmed at autopsy (case 41).

We are able to present this unusually large series chiefly because the Montefiore Hospital is an institution for chronic diseases. There are in its wards many elderly persons suffering with debilitating illnesses in advanced stages, and such persons are particularly likely to have oil pneumonia. This is reflected in the fact that in our postmortem group the average age of the patients (at death) was 61.8 years as compared with 53.6 years, the average age of the patients previously reported on. Patients in the neurologic service, in whom the frequency of dysphagia makes oil aspiration pneumonia a common complication, form a younger age group. Thus, the average age of our 6 clinical patients is 35 years, and that of 5 similar "neurologic patients" in the group studied post mortem was 45.4 years.

Liquid petrolatum was by far the most important etiologic agent in the production of this condition in our series and in the cases of the 58 adults described in the literature. In the latter group this substance was definitely the etiologic agent in 47. In 9 additional cases the oil

11 Liquid petrolatum stains a pale orange with scarlet red and pink with Nile blue sulfate and if uncontaminated by other fats and oils does not reduce osmic acid. On extraction from tissue it can be readily identified by its high boiling point, its failure to saponify and its negative reaction to the acrolein test.

was not identified and no definite history was available, and it is therefore not possible to determine in how many of these the condition may also have been due to liquid petrolatum. Among our cases there was 1 (case 19) in which much of the alveolar exudate was necrotic and contained scattered macrophages together with oil which reduced osmic acid but was not further identified. The patient, however, had been receiving liquid petrolatum by mouth, and there was some evidence of this oil in the lung as well. In 2 cases in which extensive liquid petrolatum pneumonia with superimposed infectious bronchopneumonia was present, a few of the alveoli contained similar necrotic exudate, suggesting the presence of an animal fat or oil probably originating in the food. In 2 additional cases, in which liquid petrolatum had been used together with cod liver oil and glycerin respectively, there was no discernible evidence to indicate that the latter two substances had played any part in the development of the lesions. Most of the patients in this series were known to have been habitual users of liquid petrolatum in relatively large quantities. The oil had been taken by mouth, intranasally (as drops, sprays, packs or douches) or intratracheally (usually as a lubricant in cases of tracheotomy), the frequency of the various routes is indicated in table 1. It will be noted that the incidence of use of the oral route among our patients is comparatively high. This is easily explained by the fact that oil is commonly used as an intestinal lubricant by chronic invalids. This may well have been the method of administration employed by our 6 patients for whom the route is listed as unknown, since most of these gave histories of having used "laxatives" habitually prior to admission to the hospital. The 1 patient by whom the intratracheal route was used employed a petroleum jelly to lubricate an operative stoma and a tracheotomy tube.

The fats and oils of animal origin which play such a significant part in the production of this condition in infants and young children are of much less importance in the case of adults. Cream was the etiologic agent in the case reported by Thomas and Jewett,¹² and cod liver oil was the causative factor in another.¹³ Vegetable oils, particularly the iodized poppyseed oil and iodized sesame oil used in bronchography, are rare offenders, as they are chemically nonirritating, in addition, they are used in relatively small quantities and are frequently absorbed or expectorated rapidly. That such elimination can occur even in the presence of pulmonary lesions due to liquid petrolatum was demonstrated in the cases of 2 of our patients for whom bronchographic

12 Thomas, W. S., and Jewett, C. H. Pneumonia Following Aspiration of Fats from the Esophagus Dilated as a Result of Cardiospasm, *Clifton M. Bull.* **12** 130 (Dec.) 1926.

13 Young, A. M., Applebaum, H. S., and Wasserman, P. B. Lipoid Pneumonia, *J. A. M. A.* **112** 2406 (June 10) 1939.

examinations were made. Bezançon, Delarue and Valet-Bellot¹⁴ performed autopsies on 3 patients who died two days, twelve days and six years respectively after the intratracheal administration of this oil, and noted slight phagocytosis of the oil in the interstitial tissue but

TABLE 1—Routes of Administration of Oil to Adult Patients

Author	Route of Administration						
	Cases Reported	Autopsy Performed	Oral	Nasal	Oral and Nasal	Intra tracheal	Unknown and Unreported
Laughlen ³	1	1	1				
Thomas and Jewett ¹²	1	1	1				
Fischer Wasels, B Todliche Lungen schrumpfung durch Gebrauch von Men- tholol, Frankfurt Ztschr f Path 44 412, 1933	1	1		1			
Bodmer, H, and Kallos, P Ueber schwere Lungenschadigung (Lungenzirrhose) in folge Aspiration von Paraffinol bei thera- peutisches Anwendung, Arch f Ohren, Nasen- u Kehlkopf 136 40 (April) 1933	1	0		1			
Meursing, F Pneumonoliposis, Nederl tijdschr v geneesk 77 3878 (Aug) 1933	2	2					2
Ellinger, E Paraffinol-schadigung der Lunge, Fortschr a d Geb d Rontgen strahlen 49 397 (April) 1934	3	1				3	
Hayes and Gardner ^{2a}	2	2		2			
Grayzel, D M, and DuMortier, J J Pneu- monia in Children Following Aspiration of Oil and Fat, Yale J Biol & Med 6 599 (July) 1934	1	1	1				
Graef, I Pulmonary Changes Due to As- piration of Lipids and Mineral Oil, Am J Path 11 862 (Sept) 1935	3	3	2				1
Ball, F E Petroleum Oil Pneumonia in an Adult, Illinois M J 69 62 (Jan) 1936	1	1	1				
Davis, K S Mineral Oil in the Lung, Radiology 26 131 (Feb) 1936 *	3	1		2		1	
Tchertkoff, I G, and Ornstein, G G Bronchopulmonary Disease Attributed to the Use of Intranasal Instillation of Oily Substances, Quart Bull, Sea View Hosp 1 139 (Jan) 1936	9	0		9			
Ritchie ^{2b}	10	10	6		1		3
Ikedu ¹⁰	5	5	1	3			1
Fetterman ¹⁴	2	2	2				
Paterson ⁹	6	6					6
Ellinger ²⁴	3	1				3	
Walsh and Cannon ²¹	3	3		2			1
†Young, Applebaum and Wasserman ¹³	1	1	1				
Literature (total)	58	42	16	20	1	7	14
This series (postmortem group)	41	41	29	3	2	1	6
This series (clinical group)	6	0	4		2		
Total	105	83	49	23	5	8	20

* One of these cases was also reported by Houck, G M Intratracheal Instillation of Liquid Petrolatum Pulmonary Injury Therefrom, California & West Med 49 187 (Sept) 1938 Footnote 1c

† This case was previously cited by Kline, B S Pathology of Chronic Non-Tuberculous Inflammations of the Lung, Am Rev Tuberc 38 663 (Dec) 1938

little other histologic reaction. It appears, however, that iodized poppy-seed oil can produce reactions under exceptional circumstances. Rabino-

14 Bezançon, F, Delarue, J, and Valet-Bellot, M Le sort du lipiodol dans le parenchyme pulmonaire chez l'homme, Ann d'anat path 12 229 (March) 1935

vitch and Lederer¹⁵ mentioned a case in which the changes seen at necropsy were those associated with lipoid pneumonia. Wright¹⁶ reported another in which a granuloma was produced by oil trapped by a bronchial neoplasm. In the latter case the appearance resembled the normal walling off of a foreign body that cannot be removed rather than a reaction attributable to the chemical nature of the oil. Ordinarily vegetable oils induce little or no macrophagic response.

It has been repeatedly demonstrated that oil introduced into the pharynx is capable of entering the bronchial tree without exciting reflex inhibition. Quinn and Meyer¹⁷ instilled iodized poppyseed oil into the nose during sleep and found that it quickly entered the trachea and bronchi. Pirie¹⁸ mentioned a comparable experiment. Experimental work on animals¹⁹ also seems to demonstrate the fact that liquid petrolatum, being bland and nonirritating to the pharyngeal mucosa, does not stimulate reflex closure of the glottis and fails to elicit a cough reflex. In addition, it hinders ciliary activity by mechanically slowing up or stopping the stream of mucus normally set up by the beat of the cilia.²⁰ Aspiration of the oil is thus favored by the ease with which it can enter the respiratory passages and by interference with the protective mechanisms designed to expel foreign matter from them.

These considerations are important in the genesis of oil pneumonia in infants and in adults who either habitually use oil intranasally or into whose nostrils oil is introduced during somnolent or irrational states. Thus, in Walsh and Cannon's²¹ cases 2 of the patients were apparently healthy men who had been using oil intranasally and died by suicide, and a third was a young comatose girl into whose conjunctival sacs oil was repeatedly introduced. In adults who take oil orally, pathologic processes which interfere with normal cough, palatal or swallowing reflexes become important predisposing factors. The condition is therefore frequently encountered in debilitated, recumbent and aged persons, in persons with dysphagia of nervous origin and in patients in whom

15 Rabinovitch, J, and Lederer, M. Lipoid Pneumonia, *Arch Path* **17** 160 (Feb) 1934

16 Wright, R. D. Reaction of Pulmonary Tissue to Lipiodol, *Am J Path* **11** 497 (May) 1935

17 Quinn, L. H., and Meyer, O. O. Relationship of Sinusitis and Bronchiectasis, *Arch Otolaryng* **10** 152 (Aug) 1929

18 Pirie, A. H., in discussion on Pierson, J. W. Some Unusual Pneumonias Associated with the Aspiration of Fats and Oils, *Am J Roentgenol* **27** 572 (April) 1932

19 Ikeda^{1a} Laughlen³

20 Proetz, A. W. Effects of Certain Drugs on Living Nasal Ciliated Epithelium, *Ann Otol, Rhin & Laryng* **43** 450 (June) 1934

21 Walsh, T. E., and Cannon, P. R. Problem of Intranasal Medication, *Ann Otol, Rhin & Laryng* **47** 579 (Sept) 1938

neoplastic or other destructive processes involve the mouth and throat. The nonirritating character of the oil makes its aspiration by such persons particularly likely, although occasionally other substances and food particles may be aspirated as well. Finally, tracheotomy may predispose to the condition if the oil (or other petroleum product) is used for lubrication of the airway.

Once aspirated, the disposition of the oil in the lung appears to depend almost exclusively on mechanical factors. In a study of pulmonary inspiration and aspiration of fluid in rabbits and dogs, Corper,²² using india ink, found that the substance was patchy in its localization and showed a tendency toward immediate aspiration into the alveoli. It seemed probable to him, on the basis of his experiments that the disposition of the fluid is dependent entirely on gravity and inspiratory suction. The importance of gravity as a prime factor in determining the position of the lesions is further borne out by the work of others. Walsh and Cannon²¹ injected oil into the nasal passages of rabbits held in the sitting and in the vertical position and found in each instance localization of the oil in the lowermost portions of the lungs. A study of our own postmortem series confirms these conclusions. Thus, the lower lobe of the right lung was involved in 34 instances, the lower lobe of the left in 29, the middle lobe of the right in 25, the upper lobe of the right in 16 and the upper lobe of the left in 13. It is evident from these figures that the dependent portions of the lungs are predominantly involved and that the right lung is more often involved than the left. In addition, the lower portions of the individual lobes are most often affected. In only 2 instances were the upper lobes alone involved. In 11 patients involvement of the upper lobes was part of an extensive process, although in 1 of these the process began in the upper lobe of the right lung, as was proved by roentgen examination (case 27).

PATHOLOGIC PICTURE

The response of the lung to the aspiration of liquid petrolatum is twofold. A macrophagic reaction characterizes the early stages and occurs very promptly. This is followed and gradually replaced by fibrous proliferation of the interstitial tissue, which develops much more slowly and appears to be in large measure a foreign body reaction. As the lesion increases in size, the fibrosis becomes more and more prominent, and at the same time the macrophages tend to disappear.

The initial response is characteristic. Phagocytes accumulate in large numbers in the alveolar spaces, where they quickly take up the oil which is present there in a rather fine state of subdivision. The numerous droplets of varying size give the cells, if small, a foamy appearance or,

²² Corper, H. J. Pulmonary Aspiration of Particulate Matter, Normally and During Anaesthesia, *J. A. M. A.* **78** 1858 (June 17) 1922.

TABLE 2—Group Studied Post Mortem

Patient	Age at Death	Major Diagnosis	Time in Hospital	Etiologic Agent			Predisposing Factors	Pulmonary Symptoms	Pulmonary Signs	Roentgen Examination of Chest	Autopsy		
				Time Taken (Min)	Oil	Route					Involvement	Gross Appearance	Microscopic Appearance
1 M C	45	Multiple sclerosis	14 yr	5 yr	Oral	Oral	Dysphagia	3 episodes of bronchopneumonia, chronic cough	Dulness rales and bronchial breath sounds in R L L, and L L L	"Positive"	All lobes	Massive, firm velvety low brown consolidation	Oil pneumonia in all stages oil in hilar node
2 L L	66	Carcinoma of rectum	2 yr	2 yr	Liquid petrolatum	Oral	Recumbency	None	None		L L L * L U L	Firm, nodular small gray areas white fluid exudate	Moderately advanced to advanced oil pneumonia
3 B S	64	Carcinoma of stomach	4 mo	3 mo	Liquid petrolatum	Oral	Recumbency	None	Dulness and diminished breath sounds at both bases no other signs		Base of R U L	Discrete, firm gray consolidated areas	Moderately advanced to advanced oil pneumonia
4 N B	57	Diabetes, residual hemiplegia	4 yr	4 yr	Liquid petrolatum	Oral	Paralysis of hypoglossal nerve	None	None		All lobes	Scattered, small firm gray areas, white fluid exudate	Early oil pneumonia, bronchopneumonia, congestion
5 J G	60	Carcinoma of tongue	10 mo	2 mo	Liquid petrolatum	Oral	Dysphagia oral pathologic condition	None	None	No abnormality †	All lobes	Firm, yellow areas of consolidation	Early to moderately advanced oil pneumonia
6 L S	66	Arteriosclerosis coronary occlusion	1 yr	7 mo	Liquid petrolatum	Oral	Weakness	None	Dulness rales and bronchial breath sounds in R L L, R M L	No abnormality †	All lobes	Upper lobes fibrotic and gray, lower lobes mottled, yellow gray consolidation purulent foci	Early to moderately advanced oil pneumonia bronchitis bronchiolitis
7 N C	79	Carcinoma of cheek	2 yr	3 mo	Liquid petrolatum	Oral	Dysphagia oral pathologic condition	None	None	"Positive"	R L L	Large, gray, consolidated areas yellow fluid exudate	Early to advanced oil pneumonia bronchopneumonia
8 M S	75	Carcinoma of cecum	4 mo	2 wk	Liquid petrolatum	Oral	Recumbency	None	None	No abnormality †	R U L R M L R L L L L L	Small, firm, nodular pinkish to dirty gray areas with surrounding consolidation in lower lobes	Early to advanced oil pneumonia, few small areas of necrotic exudate (food fat?) bronchopneumonia
9 J L	55	Dermatitis vegetans	1 yr	7 mo	Liquid petrolatum	Oral	Recumbency	None	None		R M L	Firm, discrete pea sized gray nodules	Advanced oil pneumonia (paraffinoma)

10 Y S	66 T	Tuberculosis of spine	4 yr	Liquid petrolatum	4 yr	Oral	Recumbency	None	Bilateral basal rales	No abnormality †	R L L L L L	Firm, yellow gray areas containing purulent foci, surrounding diffuse red gray consolidation	Early to advanced oil pneumonia bronchitis, patchy bronchopneumonia
11 M M	82 M	Carcinoma of rectum	3 wk	Liquid petrolatum	3 wk	Oral	Recumbency	None	None		R U L R M L R L L L L L	Firm, gray, mottled areas of consolidation	Early to moderately advanced oil pneumonia bronchopneumonia
12 M H	72 M	Carcinoma of larynx	2 mo	Liquid petrolatum	2 mo	Tracheotomy tube	Tracheotomy	None	None	No abnormality	R L L L L L	Firm consolidation, congestion	Early oil pneumonia
13 M S	67 M	Arteriosclerosis coronary occlusion	2 yr	Liquid petrolatum	6 mo	Oral	Recumbency	None	Dulness rales, friction rub at right base	"Positive"	R L L L L L	Firm, yellow, patchy consolidation thrombus in left pulmonary artery	Moderately advanced oil pneumonia bronchopneumonia
14 M B	53 M	Hypertension cerebral thrombosis	1 yr	Liquid petrolatum glycerol	9 mo	Oral	Weakness	Low grade fever	Dulness bronchial breathing rales	"Positive"	R M L R L L L U L	Firm, dirty gray yellow areas of consolidation	Early to moderately advanced oil pneumonia patchy bronchopneumonia
15 B A	54 M	Amyotrophic lateral sclerosis	10 mo	Liquid petrolatum	4 mo 1 yr	Oral	Dysphagia	None	Rales diminished at both bases		R L L L L L (bases)	Irregular, brownish yellow areas of consolidation	Early oil pneumonia, bronchopneumonia
16 B F	87 F	Carcinoma of larynx	1 mo	Liquid petrolatum	3 wk	Nasal	Recumbency	None	None		R L L (base)	Pea sized, firm yellow areas	Early oil pneumonia
17 D G	68 M	Nonunited fracture of femur	6 yr	Liquid petrolatum	5 yr	Oral	Recumbency	None	Increased fremitus rales diminished breath sounds	"Positive"	R M L R L L L L L	Rt —Granular, gray white, firm, tissue Empyema Lt — Dirty gray consolidation	On right, advanced oil pneumonia (paraffinoma) on left moderately advanced oil pneumonia bronchopneumonia
18 A B	79 F	Carcinoma of rectum	1½ yr	Liquid petrolatum	15 mo	Oral	Weakness	Low grade fever	None	"Positive"	R L L L L L	Nodular, firm gray areas of consolidation	Early to moderately advanced oil pneumonia
19 P L	74 M	Carcinoma of stomach	2 mo	Liquid petrolatum	1 mo	Oral	Dysphagia vomiting marked recumbency	None	None	No abnormality †	L U L L L L (bases)	Firm, dull, gray to red gray areas of consolidation excluded	Areas of necrotic exudate with partially disintegrated lipophages some fibrosis few areas contain oil filled macrophages no necrosis most of oil reduced osmic acid bronchopneumonia in R U L

TABLE 2—Group Studied Post Mortem—Continued

Patient	Age at Death, Sex	Major Diagnosis	Time in Hospital	Etiologic Agent			Predisposing Factors	Pulmonary Symptoms	Pulmonary Signs	Roentgen Examination of Chest	Autopsy		
				Time Taken (Minimal)	Oil	Route					Involve ment	Gross Appearance	Microscopic Appearance
20 M G	39	Carcinoma of breast	5 mo		Liquid petrolatum	Oral	Recumbency	Low grade fever	Rales diminished breathing at right base	No abnormality	R U L R L L (bases)	Firm, bright yellow areas of consolidation	Early oil pneumonia (tumor in lymphatics)
21 A B	55	Rheumatoid arthritis rheumatic heart disease	5 yr	5 yr	Liquid petrolatum	Oral	Recumbency	Chronic cough	None	"Positive"	R M L	Firm gray nodules thick fluid exudate fibrinous pleurisy	Moderately advanced to advanced oil pneumonia
22 M H	68	Carcinoma of palate	6 mo	Months	Liquid petrolatum	Nasal	Oral pathologic condition	Chronic cough	Dulness bronchial breathing	"Positive"	R M L L L L	On right, firm gray consolidation oil exuded on left, pea sized firm granular areas	Moderately advanced to advanced oil pneumonia (paraffinoma) congestion
23 L G	69	Hypertension coronary occlusion	4½ yr	1½ yr	Liquid petrolatum	Oral	Weakness	Chronic cough	Rales at both bases	"Positive"	All (only bases of upper lobes)	Extensive, firm, gray areas of consolidation purulent exudate in bronchi	Early to moderately advanced oil pneumonia marked congestion
24 E O	23	Postencephalic parkinsonism	8 yr	10 mo	Liquid petrolatum	Oral	Weakness	None	Dulness rales		R M L R L L L L L L U L	Granular, gray yellow diffuse areas of consolidation with purulent foci	Early to moderately advanced oil pneumonia oil in hilar nodes
25 J R	59	Carcinoma of colon	1 yr	11 mo	Liquid petrolatum	Oral	Weakness	Low grade fever	Basal rales on right	"Positive"	R L L L L L	Firm, gray white walnut sized nodules tuberculosis in upper lobes	Moderately advanced oil pneumonia bronchitis patchy bronchopneumonia
26 A H	60	Hypertensive heart disease	11 mo	Many years, 15 mo	Liquid petrolatum	Nasal, Oral	None	Chronic cough low grade fever	Loud bronchial breathing at base of left lung	"Positive"	R M L R L L L L L	Firm consolidation and fibrosis oil exuded obliterated right pleural space, moderate bronchiectasis of lower lobes lobar pneumonia in L U L	Moderately advanced to advanced oil pneumonia patchy bronchopneumonia oil in hilar nodes
27 L K	42	Scleroderma	29 yr	10 yr	Liquid petrolatum, cod liver oil	Oral	Difficulty in opening mouth	Chronic cough pain in chest low grade fever several episodes of bronchopneumonia	Dulness bronchial breathing rales	"Positive"	R U L R M L R L L	Firm, gray consolidation with fibrous strands purulent foci, pleural adhesions	Advanced oil pneumonia (paraffinoma)
28 D W	70	Hypertension, hemiplegia	3 yr	20 mo	Liquid petrolatum	Oral	Recumbency	Chronic cough	Rales bronchial breathing at R L L	"Positive"	R U L R L L L L L	Firm, granular gray consolidation purulent foci slight bronchiectasis healed apical tuberculosis	Early to moderately advanced oil pneumonia bronchitis with slight bronchopneumonia

29 J R	55 F	Arteriosclerosis hyperten	1½ yr	Liquid petrolatum	4 mo	Oral	Weakness	Chronic cough low grade fever several epi sodes of broncho pneumonia	Dulness rales increased fre quency bron chial breathing	No abnor mality †	All (bases of upper lobes)	Yellow to yellow pink granular con solidation puru lent foci	Moderately advanced to advanced oil pneu monia few small areas of necrotic exudate (food fat?) bronchiolitis bron chopneumonia
30 W L	63 M	Carcinoma of lung	1½ yr	Liquid petrolatum	7 mo	Oral	Weakness	Chronic cough	Dulness dimin ished breath sounds	"Posi tive"	L U I (lower outer part)	Firm, gray, tumor like consolidation tumor in R L L	Moderately advanced to advanced oil pneumonia
31 A G	53 M	Chronic ante rior poliomye litis	17 yr	Liquid petrolatum	17 yr	Oral	Recumbency	Chronic pain in chest	Dulness rales diminished breathing		R M L R L L (bular) L L L	On right, firm con solidation with puru lent foci on left patchy consolidation	Early to moderately advanced oil pneu monia advanced (paraffinoma) in a few small areas marked congestion
32 A G	63 F	Arterioscle rotic heart disease	1 wk	Liquid petrolatum	1 wk	Oral	Recumbency	None	None		R L L L L L	Areas of pale con solidation	Early to moderately advanced oil pneu monia broncho pneumonia (early)
33 N W	72 M	Arterioscle rotic heart disease	1 mo						Dulness dimin ished breath sounds	"Posi tive"	R M L R L L L L L	Firm, gray fibrous tissue, bronchec tasis	All stages of oil pneu monia, advanced stage (paraffinoma) most prominent
34 I H	62 M	Arteriosclero sis subarach noid hemor rhage	2 days								R U L R M L R L L (bases)	Firm, pale yellow gray masses	Early to moderately advanced oil pneu monia broncho pneumonia
35 M M	76 M	Carcinoma of maxillary sinus	18 days				Oral pathologic condition	None	None	"Posi tive"	R M L R L L (adjoin ing por tions near hilus)	Firm, pale gray tis sue, well circums cribed, fibrosis in R L L, obliterated pleural space	Moderately advanced to advanced oil pneu monia (paraffinoma) bronchopneumonia
36 R K	79 F	Hypertension hemiplegia	3 wk	Liquid petrolatum			Recumbency	Chronic cough per sistent pain in chest	Dulness rales increased fremitus	"Posi tive"	R L L	Firm, gray mass, oil exuded, bronchec tatic abscess in L U L	Advanced oil pneu monia (paraffinoma)
37 C S	81 M	Carcinoma of floor of mouth	3 days				Oral pathologic condition		Rales bron chial breathing		R M L R L L L U L L L L (adjoin ing por tions)	Gray white and yel low white firm con solidation yellow, frothy fluid exudate	Moderately advanced to advanced oil pneu monia bronchopneu monia in R L L

TABLE 2—Group Studied Post Mortem—Continued

Pa- tient	Age at Death	Major Diagnosis	Time in Hos- pital	Etiologic Agent			Pulmonary Symptoms	Pulmonary Signs	Roentgen Examina- tion of Chest	Autopsy		
				Oil	Time Taken (Min- mal)	Route				Involvement	Gross Appearance	Microscopic Appearance†
38 F L	59 M	Carcinoma of esophagus	4 mo				Chronic cough low grade fever	Rales bron- chial breathing	'Posi- tive'	R M L R L L R U L (base)	R U L showed nodu- lar areas of pale con- solidation, others, diffuse pink gray consolidation	Early to moderately advanced oil pneu- monia broncho- pneumonia
39 S C	58 M	Carcinoma of stomach	6 mo	Liquid petrolatum		Oral	None	Rales	No abnor- mality †	L L L R L L?	Granular, dirty pink gray consoli- dation of L L L, empyema on right lower lobe small and fleshy	Moderately advanced oil pneumonia bronchopneumonia
40 S B	44 M	Tumor of brain	5 mo	Liquid petrolatum		Oral	Chronic cough	Rales		All	Firm gray to white areas of consoli- dation in nodular groups	Moderately advanced to advanced oil pneu- monia, broncho- pneumonia
41 S M	56 M	Degenerative olivopontocere- bellar disease	3 yr	Liquid petrolatum	2½ yr	Oral	Repeated (3) episodes of broncho- pneumonia	Dulness rales increased fre- mitus	"Posi- tive"	R U L R M L R L L L L L	Firm gray to pink gray consolidation, fluid containing oil exuded on compres- sion, hilar nodes enlarged	Moderately advanced to advanced oil pneu- monia (paraffinoma), bronchopneumonia

* In this table the following abbreviations are used L U L, upper lobe of left lung, R U L, upper lobe of right lung, L L L, lower lobe of left lung R L L, lower lobe of right lung, and R M L, middle lobe of right lung

† Roentgen examination on or soon after admission, inadequate or no follow up

Key to description of microscopic findings

Early—Numerous lipophages, little or no septal proliferative reaction varying grades of edema and congestion

Moderately Advanced—Lipophages numerous or diminishing moderately advanced proliferative reaction, frequently with many cells, giant cells in varying numbers, frequent alveolar distortion and epithelialization

Advanced—Lipophages few or absent, dense fibrosis with moderate or slight cellularly Paraffinoma Dense fibrosis with entrapped oil filled spaces replacing normal parenchyma.

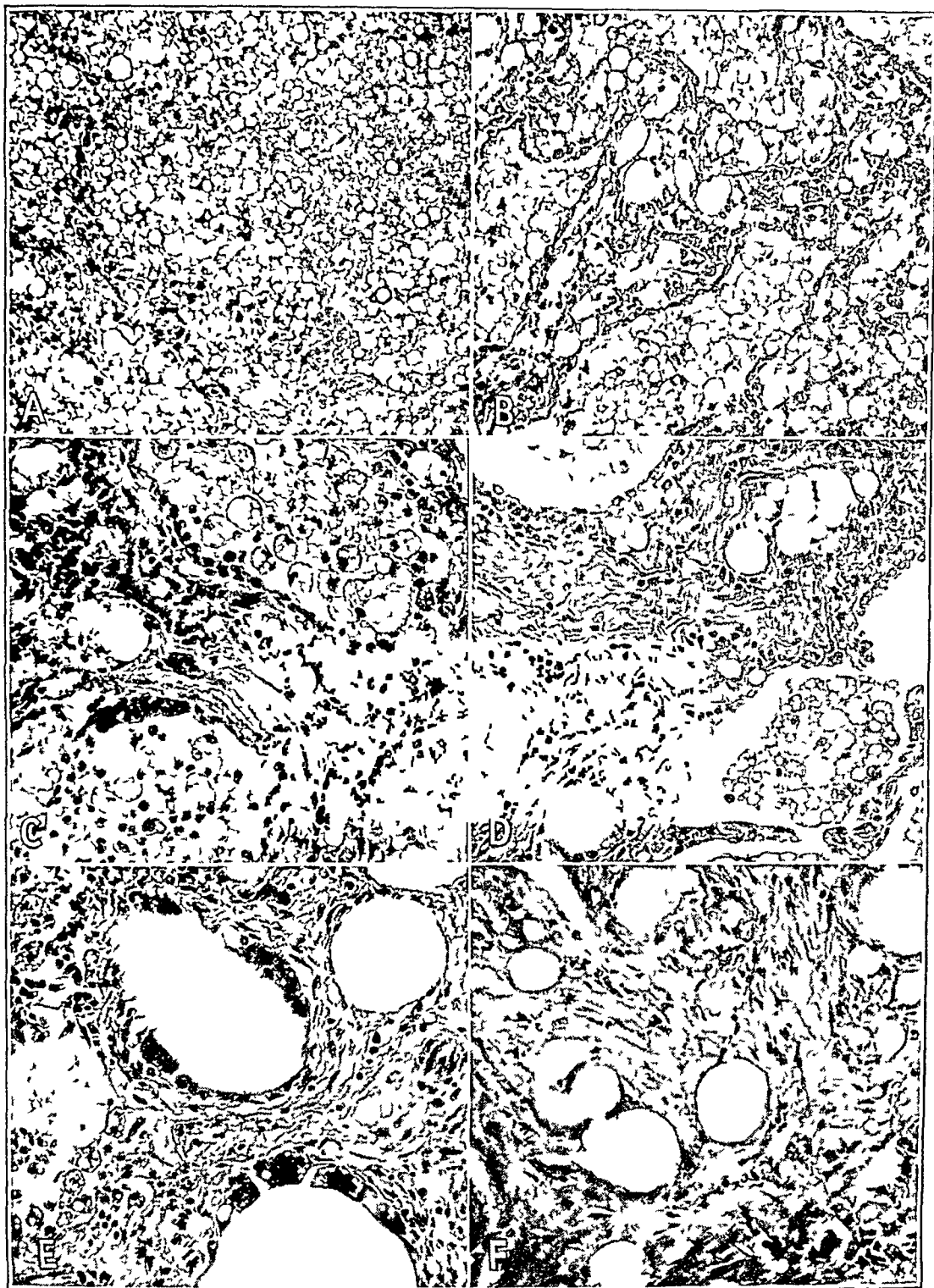


Fig 1—Stages in the progress of the pulmonary lesion caused by aspirated liquid petrolatum ($\times 139$) *A*, early process The alveoli are crowded with oil-filled macrophages There is septal congestion but no fibrosis *B*, extensive infiltration of the septums and lymphatics with macrophages, in many of these the oil globules have coalesced to form one large droplet *C*, increasing septal fibrosis with entrapping of oil Note the epithelization of the alveoli *D*, later stage *E*, oil-filled spaces with crescent giant cells at the periphery Note the oil droplets in the cells *F*, paraffinoma

if large, a resemblance to ordinary fat cells. These are so-called lipoid cells, or lipophages. The intracellular droplets, seen by ordinary staining methods as vacuoles, are practically always well defined, the cell membrane is sharply outlined, and the cell nucleus is frequently distorted and displaced peripherally. Extracellular oil is usually present, becoming more prominent in later stages as the macrophages disintegrate. The alveolar septums may show considerable edema and some cellular infiltration if irritating medicaments have been aspirated with the oil (as when nasal sprays have been used), if organic oils or fats of animal origin have been aspirated as well or if there is associated infection. In the presence of bronchopneumonia, congestion and polymorphonuclear infiltration are prominent features.

Grossly, at this stage the involved portions of the lung are gray, gray-yellow or bright yellow, are often mottled and are moderately firm, with a spongy texture. They protrude slightly above the level of the surrounding parenchyma, and in the absence of secondary infection are usually sharply demarcated, a small amount of milky fluid may often be expressed from the surface. Unfortunately bronchopneumonia, bronchitis, pulmonary edema and chronic passive congestion are frequently present, and the entire area often has an appearance so muddy and congested that correct diagnosis is practically impossible without microscopic examination. The lesions may vary in size and distribution from pea-sized or smaller patches in one or more lobes to massive consolidation of both lungs, depending on the amount of oil aspirated and the frequency of aspiration.

As the secondary, or proliferative, reaction develops, the lesions gradually grow firmer and tend to become gray-white. Such advanced lesions may have the appearance of tumor tissue, for which they are not infrequently mistaken, and vary in size from small nodules, usually multiple, to large, firm masses involving almost an entire lobe or portions of two adjoining lobes. Oil may be readily scraped from the cut surface, and if bronchitis or bronchiolitis is present there may be a purulent exudate as well.

Microscopically, the proliferative reaction does not differ essentially from that associated with chronic interstitial pneumonitis due to other causes. In the later stages, in fact, when the lipophages are no longer seen, it is only by the finding of the oil entrapped within the dense fibrous tissue (and demonstrable by special staining or extraction), together with the presence of earlier stages of the same process in surrounding areas, that the cause can be determined. The fibrosis is at first slight, the septums are invaded by fibroblasts, plasma cells, lymphocytes and histiocytes. Oil-laden phagocytes are noted in the septums and the lymphatics very early, being sometimes so numerous that it is almost impossible to distinguish between the septum and the alveolar space.

Free oil, believed to come from disintegrated macrophages, is also seen. Part of this oil may eventually be carried to the regional lymph nodes, where it can be demonstrated, and oil has also been reported as occurring in other organs of the body, notably the spleen. Lipophages and free oil may also be seen in the small bronchioles which frequently are dilated and the seat of purulent infection.

With the advancing fibrosis the alveoli become distorted and the appearance of the lesion becomes less and less specific. Giant cells of the foreign body type, accumulations of lymphocytes and epithelization of the walls of the alveolar spaces²³ are often seen and indeed may appear much earlier. Tubercle-like structures are occasionally present. Accumulations of oil may give the appearance of small islands of adipose tissue, and crescent-shaped giant cells, often containing oil droplets, may be seen at the periphery of oil-filled alveolar remnants. With the increasing fibrosis the cellularity diminishes, and there finally remains only a mass of hyalinized fibrous tissue with entrapped oil, a true paraffinoma. Occasionally small deposits of calcium are seen.

Although the entire process in any given case may be in the same or almost the same stage of development, this appears to be the exception rather than the rule. Since oil has usually been administered over a period of years and has been aspirated in small quantities at more or less frequent intervals, the pathologic picture is that of a group of lesions rather than of a single one. Not only may lesions in various portions of the lung differ markedly if the oil that produced them was aspirated on separate occasions, but with equal frequency well defined and widely different stages are seen in contiguous microscopic fields. In several of our cases, in fact, the probable pathogenesis of the condition could be reconstructed from the changes observed in a single section.

CLINICAL CONSIDERATIONS

No specific symptoms or signs are characteristic of oil pneumonia. In many instances the disease is entirely asymptomatic, attention being drawn to the diagnosis by puzzling conditions in the chest observed on physical or roentgen examination. Much more frequently the condition remains entirely unsuspected during life and is discovered at autopsy.

23 The presence of low or high cuboidal cells lining the alveolar spaces (so-called epithelization) is usually a prominent feature but is by no means specific. It is seen in many other chronic pulmonary conditions, and its origin remains in doubt. Some authors feel that it represents true epithelization of the alveoli with cells originating in the terminal bronchioles, a view subscribed to by Ikeda (*Oil Aspiration Pneumonia [Lipoid Pneumonia]*, *Am J Dis Child* **49** 985 [April] 1935, *Lipoid Pneumonia of Adult Type [Paraffinoma of Lung]*, *Arch Path* **23** 470 [April] 1937).

TABLE 3—Group Studied Clinically

No	Age, Sex	Major Diagnosis	Etiologic Agent			Predisposing Factors	Pulmonary Symptoms	Pulmonary Signs	Roentgen Appearance
			Time in Hospital	Oil	Time Taken	Route			
1 A W	20 M	Multiple sclerosis	2½ yr	Liquid petrolatum	2 yr	Oral	Severe febrile episode of 2 months' duration (8/11/38 to 10/15/38)	Dulness, bilateral posterior riles	1/19/37 Few scattered, linear infiltrations in both lower lung fields 9/12/38 Small areas of consolidation scattered uniformly in all lobes 11/21/38 Infiltrations throughout right lung except apical portion of upper lobe of right lung, infiltrations in lower lobe of left lung 3/30/39 Persistent consolidations showing distinct fibrous character
2 J W	37 M	Postencephalic parkinsonism	1½ yr	Liquid petrolatum	1½ yr	Oral	Two episodes of low grade fever lasting for a few days	Dulness rales at both bases posteriorly, mineral oil identified in sputum	10/21/37 Prominent lung markings in mesial part of right lower lung field 10/15/38 Partial consolidation of lower lobe of left lung and in right lung close to the cardiac shadow and extending to the diaphragm, irregular 'steel wool mottling,' indicating extensive fibrosis 3/30/39 No change
3 L J	43 M	Posttraumatic epilepsy	1½ yr	Liquid petrolatum	Many years, 1 year	Nasal, oral	Two episodes of mild cough and pain in right anterior part of chest	Dulness, rales at both bases posteriorly (more on right), mineral oil identified in sputum	11/24/37 No abnormality in lungs 9/21/38 Partial consolidation in right lower lung field, in cardiohepatic angle infiltrations in mesial portion of lower lobe of left lung 3/30/39 No change in infiltration
4 E F	37 F	Congenital double atresia	4 mo	Liquid petrolatum	Many years	Oral	None	None	1/10/39 Consolidation in right lower lung field, in cardiohepatic angle smaller consolidation in mesial portion of lower lobe of left lung
5 A K	41 M	Amyotrophic lateral sclerosis	2½ yr	Liquid petrolatum	2 yr, 2 yr	Oral, nasal	None	None	2/20/39 Consolidation in mesial part of lower lobe of left lung and in mesial portion of the right lower lobe extending to diaphragm 3/30/39 No change
6 I S	23 M	Multiple sclerosis	3 yr	Liquid petrolatum	2½ yr	Oral	None	None	11/22/38 Extensive consolidation in the mesial portion of right lower lung field extending to diaphragm consolidation in mesial portion of lower lobe of left lung 3/30/39 No change

Symptoms were present in about half of our patients, although their significance was often overlooked. Cough occurred in 13, being usually chronic, mild and occasionally moderately productive. Blood-streaked sputum, which has been reported by others, occurred only once in our series, but in this instance it was probably due to pulmonary infarction. Pain in the chest was infrequent and usually not severe. Intermittent fever, with a temperature often rising to 101 F daily and continuing for several weeks to months, was observed in 7 of our patients, it was apparently present only when superimposed pulmonary infection was present. The clinical course in 6 instances was characterized by repeated bouts of bronchopneumonia, such as have been described in the literature. These episodes are accompanied by cough, high fever and prostration and last a few days to several weeks, any one may be terminal.

The physical findings are those associated with any chronic pneumonitis. Dulness, harsh breath sounds, bronchovesicular or bronchial breathing and rales may be present, often at the bases of one or both lungs posteriorly. With secondary bronchopneumonia the parenchyma is more widely involved and signs of pleural effusion are occasionally found. On the other hand, physical examination may reveal no abnormality, as was the case with 16 patients in this series. Clubbing of the fingers was not observed even in the presence of other chronic pulmonary disease, and it has been described only once in the literature.²⁴

The laboratory data are occasionally helpful. The leukocyte count and the erythrocyte sedimentation rate are not affected by the oil pneumonia per se, although they may be increased by secondary pulmonary infection or by the underlying illness. The presence in the sputum of oil globules, either intracellular or extracellular, is a diagnostic aid provided liquid petrolatum can be identified chemically or by differential staining, but frequently no sputum is available. Since false positive results may be obtained in the case of any person who has recently taken oil, it is advisable to withhold all oily medication for several days before examination of the sputum is to be attempted.

The roentgen findings are of importance in the diagnosis. In the early stages the markings in the lower lung fields are exaggerated. As the lesions progress, linear and nodular infiltrations develop until finally areas of consolidation are formed. These are almost always situated at one or both pulmonary bases. They usually lie close to the cardiac shadow and extend from the hilus to the diaphragm. Rarely the process first appears in one of the upper lobes, although if administration of oil is continued the lower lobes are eventually affected. When the parenchyma is more extensively involved, infiltration may be seen extending into the infraclavicular regions. The lesion may appear as an

²⁴ Ellinger, E. Paraffinolschädigung der Lunge, *Fortschr a d Geb d Röntgenstrahlen* **57** 84 (Jan) 1938.

irregular mottling composed of linear and nodular infiltrations or as a dense, homogeneous consolidation. Serial roentgenograms may show no changes for years other than gradual shrinkage of these areas due to progressive fibrosis. Compensatory emphysema may occur in the uninvolved parenchyma of the lung. Enlargement of hilar shadows is not as prominent in adults as it seems to be in children, despite the fact that oil may be found in the hilar lymph nodes.

When secondary infectious bronchopneumonia complicates the picture the roentgen appearance is apt to be confusing. At this time the shadows are a combination of the basal lesions due to oil and the superimposed exudative reaction due to the infection, which may involve other lobes as well. In addition, pleural effusion may be present. As the process subsides the basal lesions become more distinct, persisting after the bronchopneumonic infiltrations have disappeared.

Oil aspiration pneumonia is readily confused with other chronic pulmonary lesions, particularly those involving the lower portions of the lungs. Some of these require definite therapy or affect the prognosis, and it therefore becomes important to differentiate them as far as possible. In our experience lesions due to oil have been mistakenly diagnosed as bronchiectasis, unresolved pneumonia, pulmonary metastasis, primary tumor of the lung, infarct and tuberculosis.

The clinical and roentgen appearance of bronchiectasis may be similar to that of oil pneumonia. The sputum in the former, however, is more profuse and is often foul, clubbing of the fingers is frequently present, and roentgen study with iodized poppyseed oil reveals dilated bronchi. The two conditions may, of course, coexist. Unresolved pneumonia and chronic pneumonitis of infectious origin are difficult to distinguish from the condition due to oil. It is probable, in fact, that oil is actually the cause of a considerable percentage of such lesions for which the etiologic agent has never been established.

A considerable number of our patients had malignant tumor elsewhere than in the lungs. Pulmonary shadows were likely, therefore, to be improperly interpreted as due to metastasis, particularly as the roentgen appearance may be similar. Failure of the pulmonary infiltrations to increase in size over a period of months after intake of oil has been stopped is strong evidence against a diagnosis of metastasis.

Primary pulmonary neoplasm may also be incorrectly diagnosed because of the fact that it may be indistinguishable roentgenographically and even on gross pathologic examination from oil aspiration pneumonia (particularly the advanced stages). The course of the two processes differs, however, and in most instances repeated roentgen examinations supplemented by bronchoscopic examination and biopsy will serve to differentiate them.

Shadows in the lower portions of the lungs in persons with cardiac disease may, of course, be attributable to pulmonary infarcts. Blood-

streaked sputum and sudden dyspnea in such patients favor this diagnosis. More important, however, is the fact that shadows due to infarct are usually evanescent, quickly diminishing in size, infarcts may become organized, but this is rare.

Basal tuberculosis is relatively uncommon and is almost always attended by pulmonary symptoms. On the other hand, oil aspiration pneumonia is most often present in the lower lobes and usually produces few or no symptoms. When the lesion caused by the oil is extensive and involves the upper lobes or begins in an upper lobe differentiation may be difficult. The presence of cavitation and the demonstration of tubercle bacilli in the sputum establish the diagnosis of tuberculosis, sputum negative for tubercle bacilli in the presence of large infiltrations attended by fever or other evidence of activity practically always rules it out. In general, tuberculosis is less often a source of confusion in the cases of adult patients than might be expected.

It cannot be too strongly emphasized, however, that oil pneumonia is frequently associated with these other pulmonary diseases, and in such cases differential diagnosis may be extremely difficult.

The following case histories are presented at length because of their unusual interest. The first 4 cases reported were studied post mortem, the remaining 2 were studied clinically only.

REPORT OF CASES

CASE 1—M. C., a man aged 45, was admitted to the hospital in April 1922 with multiple sclerosis of many years' duration. He had progressive bulbar involvement and dysphagia. From 1931 to 1936 he received liquid petrolatum by mouth several times weekly. In January 1933 he had an episode of dyspnea and cough, several times weekly. In January 1933 he had an episode of dyspnea and cough, his temperature rising to 103.6 F. This lasted three days. In December 1934 a second episode of productive cough and fever, with temperatures to 102.6 F, occurred, this episode lasted for seven days. At this time, dulness, bronchial breathing and rales were demonstrable bilaterally, while roentgen examination (fig. 2) revealed diffuse, mottled density made up of coalescent exudative patches involving the major portions of both lungs. No subsequent roentgenograms were taken. In February 1935 a third episode of fever occurred, with temperatures to 101 F, and lasted three days. A chronic nonproductive cough developed in November, and the man died three months later, in February 1936.

At autopsy there was massive, firm consolidation of all lobes with obliteration of fissures. On cut section the lung tissue was yellow-brown to gray-white and was spongy. Microscopic examination revealed all stages of oil pneumonia, the moderately advanced stage predominating. Oil was present in the hilar nodes.

Comment—This case illustrates massive involvement of the lungs with death probably resulting from gradual asphyxia. Dysphagia of nervous origin was the predisposing factor. Although necropsy showed no evidence of secondary infection, it is reasonable to assume that the febrile episodes were due to bronchopneumonia. Early recognition of

the condition and discontinuance of the medication might have prolonged the life of the patient

CASE 26—A H, a man aged 60 with hypertensive cardiac disease was admitted to the hospital in August 1937. He had undergone 2 "nasal sinus operations" six years previously and had been using nose drops (ephedrine in oil) daily for many years. While he was in the hospital this medication was continued, together with administration of liquid petrolatum by mouth almost every day. Physical examination on admission revealed bilateral basal rales and persistent loud bronchial breathing at the base of the left lung. Repeated roentgen examinations showed irregular areas of consolidation in the lower lobes of both lungs, close to the cardiac shadow and extending to the diaphragm, these were interpreted as due to infarction or bronchiectasis. The patient had a persistent dry cough, and his

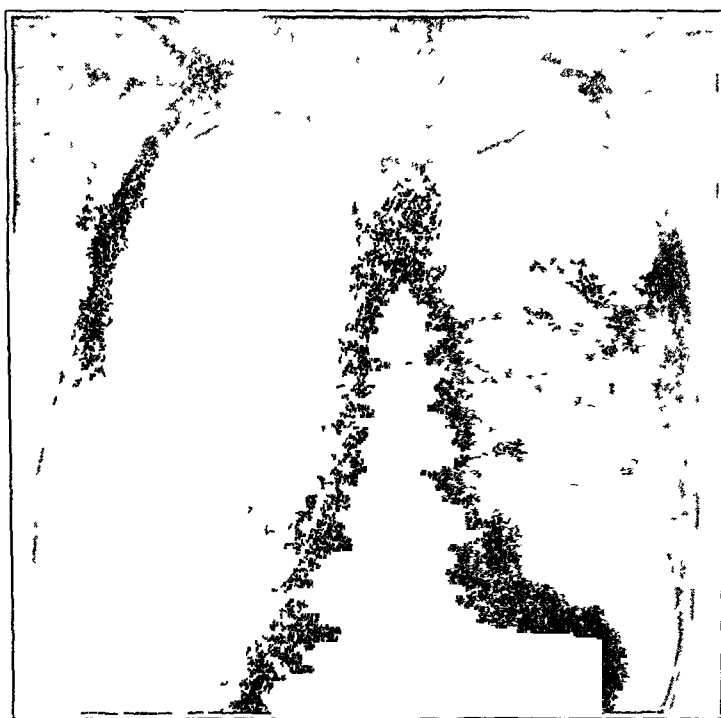


Fig 2 (case 1) —Unusually extensive oil pneumonia associated with secondary infectious bronchopneumonia

temperature was frequently elevated to 101 F. In April 1938 he complained of a sudden pain in the left side of the chest and became cyanotic and dyspneic. His temperature rose to 102 F, and he died several hours later.

At autopsy firm consolidations were present in the middle and lower lobes of the right lung and in the lower lobe of the left lung. These areas contained strands of pale fibrous tissue and exuded oil on pressure. The right pleural space was obliterated. Bronchiectasis was present in the lower lobes of both lungs. There was a massive gelatinous lobar consolidation in the upper lobe of the left lung, evidently the cause of death. Microscopic study of the middle lobe of the right lung and the lower lobes of both lungs revealed moderately advanced to advanced stages of oil aspiration pneumonia. Microscopic study of the upper lobe of the left lung revealed a picture typical of early lobar pneumonia. Oil was present in the hilar nodes.

Comment—In this case the condition was complicated by bronchiectasis, which was probably responsible for the persistent fever and, in part at least, for the cough. The puzzling thoracic findings and the history of prolonged self medication with oily nose drops should have suggested the diagnosis of oil pneumonia and brought about discontinuance of the medication. Instead, repeated aspiration of infected oil continued to carry infection into a lung already congested because of cardiac failure and little able to resist, thus undoubtedly contributing toward a fatal outcome.



Fig 3 (case 27)—Oil pneumonia involving the upper lobe and the mesial portion of the base of the right lung. There are thickening of the right transverse fissure and elevation of the diaphragm.

CASE 27—L. K., a woman, aged 42, was admitted to the hospital in September 1909 with extensive scleroderma. She had considerable difficulty in opening her mouth and was forced to eat with her head tilted far back. She received 30 cc of liquid petrolatum daily by mouth from 1924 to 1928, petrolagar daily from 1928 to 1930 and cod liver oil and liquid petrolatum frequently from 1930 to 1934. In February 1927 she had a cough with fever, the temperature rising to 104 F, this episode lasted four days. A roentgenogram of the chest taken at this time revealed consolidation involving the lower two thirds of the upper lobe of the right lung. In July 1930 she had pain in the right side of the chest, accompanied by a persistent nonproductive cough, physical examination revealed dullness, bronchial breathing and rales on the right. These signs persisted, appearing to a lesser degree at the base of the left lung. Pleural effusion developed on

several occasions, but the material was repeatedly sterile on culture and negative for tubercle bacilli by guinea pig inoculation. A tuberculin test elicited a negative reaction. Thoracic roentgenograms (fig 3) were taken on several occasions between 1930 and 1934, all revealed mottling and fibrosis in the lower two thirds of the upper lobe of the right lung, indicating nonresolution of the pneumonic consolidation seen in the 1927 film. Infiltrations gradually appeared in the right lower lobe, close to the cardiac shadow and extending to the diaphragm. The patient had several episodes of fever, the temperature rising to 102 F, and died in October 1934, during one of them. The prevailing clinical diagnosis was chronic pneumonitis, although diagnoses of tuberculosis and pulmonary neoplasm were considered for some time.

At autopsy firm gray consolidations were present in adjoining portions of the upper, middle and lower lobes of the right lung, with pale fibrous strands throughout. Numerous pleural adhesions were present, as well as purulent bronchiolitis. Microscopic examination revealed an advanced stage of oil aspiration pneumonia, chiefly paraffinoma.

Comment—Although the early clinical picture as well as the roentgen evidence strongly suggested tuberculosis, repeated bacteriologic studies failed to bear this out. A diagnosis of tumor of the lung could not long be seriously considered because of the protracted course. Familiarity with the existence of oil aspiration pneumonia as a disease entity, together with the long history of intake of oil, the presence of an obvious predisposing factor and the clinical and roentgen evidence of chronic pneumonitis, should have suggested the correct diagnosis. The symptoms are readily explained by the presence of purulent bronchiolitis and repeated bronchopneumonic episodes. Of particular interest is the initial involvement of the lower portion of the upper lobe of the right lung, probably the result of the position that had to be assumed for eating.

CASE 41—S. M., a man aged 56, was admitted to the hospital on Feb 20, 1936 with degenerative cerebellar disease, pseudobulbar palsy and dysphagia. From the time of his admission until three months before his death he received liquid petrolatum by mouth several times weekly. A roentgenogram of the chest taken on admission revealed clear pulmonary fields. In August 1937 he had a nonproductive cough, pain in the chest and fever, the temperature rising to 104 F, this episode lasted six days. Dulness, increased fremitus and rales were present at the bases of both lungs. The leukocyte count was 14,400 per cubic millimeter, with 78 per cent polymorphonuclears. A roentgenogram of the chest at this time revealed pneumonic consolidation close to the cardiac borders in the lower lobes of both lungs, together with scattered infiltrations in the upper lobe of the right lung. One month later, during an afebrile period, the physical signs were still present, roentgen examination (fig 4) revealed persistence of the consolidation in the lower lobes, the right upper pulmonary field having cleared. A second acute episode occurred in May 1938, the temperature rising to 103 F and remaining elevated for eight days. A roentgenogram of the chest revealed another area of consolidation in the upper lobe of the right lung, together with an increase in extent of the infiltrations in the lower lobe of the left lung. Another film, taken in October, revealed increasing consolidation throughout the right lung. In

order to rule out chronic suppurative pneumonitis on a bronchiectatic basis, bronchographic examination was performed on November 4, the bronchial tree was found to be normal. By November 21, evidence of iodized poppyseed oil could no longer be detected on the roentgenogram. At this time a diagnosis of oil aspiration pneumonia was made, and administration of liquid petrolatum was stopped. Examination of the sputum in January 1939 revealed oil droplets. On January 18 the patient again had a high fever, and an increase in the amount of consolidation was seen in the lower lobes of both lungs. Death occurred on January 20.

At autopsy extensive, firm gray areas of consolidation were observed in the upper, middle and lower lobes of the right lung, and in the lower lobe of the left lung. Oil-containing fluid could be expressed from the involved portions, the oil

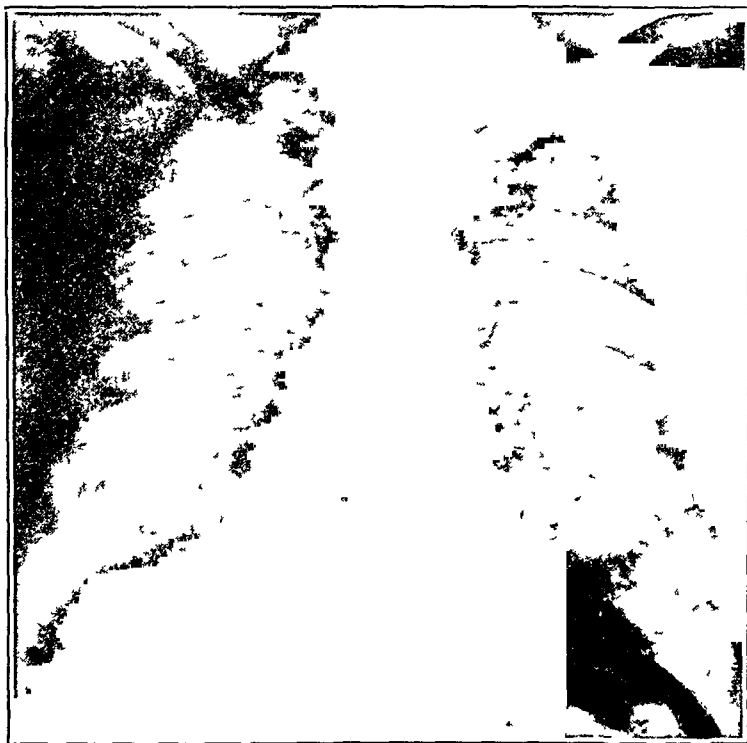


Fig 4 (case 41) —Oil pneumonia. The roentgenogram shows the basal consolidations during afebrile stage.

was chemically identified as liquid petrolatum. The upper lobe of the left lung was congested, and the hilar nodes were enlarged. Microscopically the appearance of the lesion varied from that of the moderately advanced to that of the far advanced (paraffinoma) stage. Moderate bronchopneumonia was present.

Comment —This case has several interesting features. The oil aspiration pneumonia developed while the patient was in the hospital, and the progress of the lesion was followed by roentgen examination throughout his illness. Recurrent episodes of secondary bronchopneumonia marked the clinical course, during these, symptoms referable to the lung appeared. The correct diagnosis was made clinically, although too late for the cessation of administration of oil to be effective in

changing the outcome. It is also of interest to note that iodized oil introduced into the bronchi was eliminated in spite of the extensive lesions produced by liquid petrolatum.

CLINICAL CASE 1—A W, a man aged 20, was admitted to the hospital on Nov 9, 1936, with multiple sclerosis and resultant dysphagia. He received 30 cc of liquid petrolatum by mouth three to four times weekly. A roentgenogram of the chest taken in January 1937 revealed a few scattered linear infiltrations in both lower lung fields. These were not considered clinically significant. In August 1938 the patient became acutely ill with chills, fever and respiratory difficulty, this episode lasted several weeks. The course was septic, with wide fluctuation of the temperature, which often reached 105 F. In September signs of diffuse bronchopneumonia appeared in both lungs. On September 12 a roentgenogram of the chest revealed small areas of consolidation scattered rather uniformly throughout all the lobes, this was thought at the time to represent either disseminated bronchopneumonia or hematogenous tuberculosis. The tuberculin test elicited a negative reaction, and the sputum contained no tubercle bacilli on repeated examination. The leukocyte count was 28,800 per cubic millimeter, with 84 per cent polymorphonuclears. On November 21, about six weeks after all significant fever had abated, roentgen examination showed persistence of the infiltrations throughout the lower half of the right lung and throughout the lower lobe of the left lung, most marked close to the heart. A diagnosis of oil aspiration pneumonia with superimposed secondary bronchopneumonia was made at this time. All oil medication was stopped. Follow-up roentgenograms of the chest taken as late as March 30, 1939 revealed little, if any improvement. The consolidation persisted but took on a distinct fibrous character. At present the patient is afebrile and has no symptoms referable to the respiratory tract other than a little respiratory difficulty attributable in part to disturbance in innervation of the muscles of the chest.

Comment—This case in the early roentgen manifestations closely simulated that of M C (case 1, postmortem group). The persistence of pulmonary shadows in a patient with dysphagia receiving liquid petrolatum justifies the diagnosis of oil pneumonia. As would be expected, the infiltrations have become distinctly fibrotic since discontinuation of the oil treatment.²⁵

CLINICAL CASE 4—E F, a woman aged 37, was admitted to the hospital on Jan 3, 1939, with congenital bilateral athetosis and dysphagia. She received no oily medicaments in the hospital, but she had been taking 1 tablespoonful of liquid petrolatum twice daily for many years. At no time had she had any fever or symptoms which would indicate pulmonary disease. Roentgen examination of the chest on January 10 (fig 5) revealed an area of consolidation occupying the cardio-hepatic angle of the right lower lung field, a similar lesion was present in the mesial portion of the lower lobe of the left lung. Roentgen follow-up two months later showed no change, but physical examination of the chest did not disclose any abnormalities. The sedimentation rate was normal.

Comment—This case is presented because it demonstrates all the essential features which make the diagnosis of oil aspiration pneumonia.

²⁵ Since this paper went to press, the patient died, after an ascending urinary infection. The diagnosis of oil aspiration pneumonia was confirmed at autopsy, and liquid petrolatum was identified in the lung.

possible, namely, dysphagia, a long history of intake of oil, roentgen demonstration of persistent, unchanging consolidations characteristically situated in the mesial portions of the bases of both lungs and complete absence of clinical evidence of pulmonary disease

GENERAL COMMENT

It is evident from the number of cases presented here that oil aspiration pneumonia is by no means as uncommon in adults as was previously thought. Its occurrence requires only the oral, nasal or intra-tracheal administration of oil and, in many instances, particularly when the oral route is employed, the existence of some predisposing factor



Fig 5 (clinical case 4) —Oil pneumonia. There are consolidations at the mesial portions of both pulmonary bases. There is no clinical evidence of pulmonary disease.

favoring its aspiration. Most of our patients were elderly, debilitated persons suffering with other and incurable disease. A smaller and younger group had dysphagia associated with some nervous disorder. A few patients had oral pathologic conditions which interfered with opening the mouth, chewing and swallowing. Several had nasal disease of one type or another necessitating the habitual use of intranasal medication. Finally, some had no evident predisposing condition whatever.

Liquid petrolatum was by far the most important etiologic agent, and the paucity of instances in which the pneumonia was attributable

to oils other than this, both in the cases of adults reported in the literature and in our own series, is noteworthy. Fats and oils of animal origin, such as cod liver oil and milk fat, are not forcibly administered to adults as they frequently are to weak and debilitated infants, who have, therefore, far more opportunity to aspirate such substances. Since animal oils may be extensively hydrolyzed in the lung and since both the macrophagic and the proliferative reaction are by no means as prominent as they are with liquid petrolatum, it is possible, however, that a few bona fide instances may have been overlooked or misinterpreted as simple or terminal aspiration bronchopneumonia.

Unless the pulmonary lesion produced by liquid petrolatum is so extensive that the patient dies of asphyxia, as occurred in 1 of our cases, it cannot of itself be considered a direct cause of death. Usually the patient may live for an indefinite period, until finally carried off by his primary disease or by secondary infection. Purulent bronchiolitis and bronchitis, bronchiolectasis and occasionally bronchiectasis and recurring episodes of bronchopneumonia, however, may be concomitant conditions over a considerable period. The general diminution in resistance occasioned by the debilitated state of the patient (a fact responsible for the frequency with which terminal bronchopneumonia complicates any type of chronic disease) is in part responsible for this high incidence. Other factors, however, make patients with oil pneumonia particularly susceptible to secondary bacterial invasion: the repeated aspiration of oil and other infected material and the serious interference with the normal self-cleansing action of the lung brought about by choking of the macrophages with oil, the blockage of the lymphatics, the disturbed ciliary action, the increasing fibrosis and, in some cases, the underlying chronic passive congestion.

Uncomplicated oil aspiration pneumonia is practically asymptomatic, and physical findings are of little differential value. Diagnosis of the condition must, therefore, depend on the roentgen appearance and on the history of intake of oil, often coupled with some known predisposing factor. The presence of persistent pulmonary consolidations with disproportionately slight symptoms or of infiltrations which do not fit into any well established disease pattern should suggest oil pneumonia. If the condition is kept in mind, its diagnosis is not likely to be particularly difficult.

It must be emphasized that administration of oil even in the presence of predisposing factors does not necessarily mean that oil pneumonia will occur. Liquid petrolatum is widely used without evident harm, especially by elderly persons, who are likely to have chronic pulmonary disease of other origin. We know of several dysphagic patients who

have been receiving oil but in whom no evidence of oil pneumonia has been found

By the same token, the fact that such a condition may occur in no way warrants discontinuance of the use of liquid petrolatum except, perhaps, in the nose, where it apparently serves no useful purpose. It must be realized, however, that its use is not without potential danger and that its promiscuous use by debilitated or dysphagic persons should be discouraged. Certainly, considering the total number of persons who utilize this oil, the incidence of the disease is very low indeed. It is, of course, impossible to estimate how frequently small quantities may be aspirated and adequately disposed of by expectoration and absorption as in the case of iodized poppyseed oil. Resorption of well developed lesions is believed to be not infrequent in infants, although in such cases other oils and fats are usually involved. This was not observed in any of our patients. Such reports are necessarily based on roentgen observations and cannot be corroborated. It would seem to us, in view of the pathologic process involved, that very early small lesions may be capable of resolution under good conditions but that disappearance of a lesion in the type of person in whom it is usually found is not likely to occur.

SUMMARY AND CONCLUSIONS

Oil aspiration pneumonia occurs more frequently in adults than is generally believed. A group of 47 cases with 41 autopsies is presented. All the patients were adults.

Oil pneumonia is a chronic pulmonary condition caused by aspiration of oil, usually repeated over a period of time. Liquid petrolatum is by far the most important etiologic agent in the adult.

The oil may be administered orally, intranasally or intratracheally. In this series the oral route was found to have been the one most often employed.

Aspiration is favored by the bland, nonirritating character of the oil. When the oral route is used, dysphagia and debilitated states are additional important predisposing factors.

The condition is often practically asymptomatic, and physical findings are of little differential value. Most symptoms and signs, when present, are due to superimposed infection, which is common. Diagnosis must depend on the roentgen findings, a history of intake of oil and often some known predisposing factor, occasionally oil droplets in the sputum may be identifiable and are of aid.

Persistent pulmonary infiltrations (particularly those involving the mesial portions of the pulmonary bases) which are accompanied by disproportionately few symptoms, which are more extensive than the clinical

appearance of the patient would seem to indicate oil which do not fit into any well established disease pattern, should suggest oil pneumonia.

Prognosis as to life is good so far as the oil pneumonia itself is concerned, death usually results from secondary infection or from the underlying primary illness.

The use of liquid petrolatum, particularly when self administered, is not without potential danger. Its promiscuous use intranasally and by the oral route by debilitated or dysphagic persons should be discouraged.

Dr. Max Pinner, of the Division of Pulmonary Diseases, made many valuable suggestions for this study.

BRONCHOGENIC CARCINOMA

WITH SPECIAL REFERENCE TO RESULTS WITH ROENTGEN THERAPY

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AND

GEORGE BOGARDUS, M D

CHICAGO

The increasing interest in carcinoma of the lung, which has been aroused by the rising incidence of that disease during the past three, and especially the last two decades, has brought forth many publications concerning its various features. The clinical, diagnostic, pathologic and therapeutic aspects have been classified by a number of competent observers. Recently Simons¹ in his excellent monograph "Primary Carcinoma of the Lung" exhaustively surveyed the present knowledge and opinions about bronchogenic carcinoma.

There is little or nothing new which we can add to the clinical manifestations and diagnosis of the disease from our own experiences with a fairly large group of patients. Our experiences essentially substantiate the observations of others. The data obtained on 88 patients, as shown in tables 1 to 6, are presented to round out our report and add whatever weight they may to what has already been said, rather than to raise new issues. But since we want to discuss the diagnosis in greater detail, a few of our symptomatic observations, and only those not stressed by others, may be mentioned as diagnostically important. Table 2 shows a high incidence of the symptom of loss of weight. With the success of the treatment of pulmonary cancer depending so much on an early diagnosis, that is, on diagnosis at least during the premetastatic stage, we should record that a considerable loss of weight, let us say 20 pounds (9.1 Kg) or more, usually signifies the presence of abdominal metastases. The tumor on the lung alone has not been seen to cause much loss in weight unless abscess formation has set in. Chronic hoarseness, which we found in 10 per cent of our patients, almost always means envelopment of the laryngeal nerve by the tumor mass and signifies a mediastinal invasion which is likely to render surgical

Read before the Chicago Society of Internal Medicine, April 24, 1939

From the School of Medicine of the Division of Biological Sciences, University of Chicago

1 Simons, E J Primary Carcinoma of the Lung, Chicago, The Year Book Publishers, Inc., 1937

therapy futile The significance of this symptom is enhanced if examination also reveals paralysis of the diaphragm In general, and with reference to the demand for early diagnosis, it can be said that the presence of a great number of symptoms means advanced neoplasm, that the smallest tumor causes the fewest symptoms and that therefore the task of early diagnosis of malignant tumor of the lung requires finer work than the skilful investigation only of the most pronounced symptoms, those which cause the average patient to seek medical aid

TABLE 1—*Age Distribution*

Age	Number of Patients	Per Cent of Total
30-40	3	3.4
40-50	32	36.3
50-60	31	35.2
60-70	12	13.6
70-80	9	10.2
80-90	1	1.1
	88	
Youngest patient		32
Oldest patient		82

TABLE 2—*Incidence of Predominant Symptoms*

Symptom	Number of Patients with Symptom
Cough	67
Sputum	54
Pain in chest	51
Dyspnea	32
Hemoptysis	30
Loss of weight	59
Fatigue	36
Anorexia	21
Chills and fever	15
Symptoms referable to involvement of central nervous system	13
Hoarseness	9

The chief purpose of our report is a short comment on certain therapeutic aspects of the disease Here, experiences have not been so uniform, and opinions are not so unanimous With the increasing acceptance of the disease as a frequent occurrence by the medical and lay public, there has been a steadily growing conception that this kind of cancer is cured by irradiation, chiefly by roentgen therapy This belief has become so widespread that patients in whom the disease has been diagnosed elsewhere, or merely suspected, are referred to institutions equipped for roentgen therapy, not for their confirmation of the diagnosis nor for therapeutic advice, but simply with a request for roentgen therapy On the other hand, there are a good many investigators who doubt the value of irradiation and some who disclaim all

favorable results Of the latter group, the strongest opinion was expressed by Graham² as follows

There is no record in the literature of the successful treatment by radiotherapy of a single case in which the pathologic evidence has been incontrovertible and in

TABLE 3—*Site of Tumor*

	Right Lung	Left Lung
Large bronchi		
Main bronchus	5	5
Upper	13	9
Middle	4	
Lower	3	3
Undetermined	22	5
	47	22
Peripheral location	11	8
	58	30
Total number of patients	88	

TABLE 4—*Site of Metastasis*

	Clinical Observations	Postmortem Observations
Lymph nodes		
Cervical	8	4
Tracheobronchial		14
Axillary		1
Mesenteric	1	
Long bones	8 (?)	
Vertebrae	3	3
Skull		1
Ribs		7
Chest wall	2	
Pelvis		4
Pleura	8	11
Lung (opposite)		5
Heart		1
Pericardium		3
Stomach		1
Colon		1
Liver	3	9
Pancreas		3
Kidneys		2
Spleen		1
Bladder	1	1
Peritoneum		8
Adrenal glands		10
Pituitary gland		1
Thyroid		1
Central nervous system	5	2

which a five year interval without recurrence has elapsed between the treatment and the time of reporting the case, despite the fact that many cases have been treated according to the most modern method of using both x-rays and radium. It would seem, therefore, that unless some entirely new general principle in the treatment of carcinoma is advised, the only method which can at present offer any hope is the wide surgical removal of the tumors and surrounding tissues

² Graham, E. A. Primary Carcinoma of the Lung or Bronchus, *Ann Surg* 103 1, 1936

In view of the controversy, we felt that we should examine and scrutinize our own experience in the chest division of the School of Medicine of the Division of Biological Sciences, University of Chicago, especially since we are neither surgeon nor roentgenologist and since we are not inclined by training toward either method of therapy

Since the evaluation of any treatment rests with the dependability of the diagnosis, the most rigid diagnostic standard needs to be applied

TABLE 5—*Data with Reference to Diagnostic Proof*

Specimens studied at biopsy		35
Primary tumor (bronchoscopy)	20	
Cervical lymph nodes	8	
Central nervous system (craniotomy)	3	
Chest wall	2	
Inguinal lymph nodes	1	
Pleural fluid	1	
Specimens studied post mortem		33
Total histologically proved		68
Clinical and roentgen observations accepted as sufficient for diagnosis		20
Total		88

TABLE 6—*Duration of Life After Onset of Symptoms*

Duration of Life in Months	No. of Patients Without Roentgen Therapy	No. of Patients With Roentgen Therapy
1-6	10	12
6-12	15	10
12-24	7	11
24-48	2	2
48-60	1	1
Total patients dead	35 (75.2%)	36 (85.7%)
Result unknown	9	4
Patients still living	2*	2†
Total	46	42

* One patient was living for seventeen months and 1 for twenty two months

† One patient was living for two months (therapy incomplete) and 1 for thirty months (pneumonectomy three months after the onset of symptoms was followed by roentgen therapy)

in a disease for which cures have been claimed for generations and in all parts of the body, when carcinoma may not have existed at all. As proof of a malignant neoplasm, only a microscopic examination with positive results can be accepted. The 88 patients studied, for whom data with reference to diagnostic reliability are presented in table 5, were chosen after elimination of a considerable number whose hospital diagnosis was considered as insufficiently proved. For 68 of the accepted patients the diagnosis was proved histologically, the proof for about half being obtained by the taking of a biopsy specimen either from the primary tumor by way of the bronchoscope or from extrapulmonary

metastases, for the other half the proof was obtained through post-mortem examination only. For 20 patients the diagnosis was considered as clinically established although the histologic proof was lacking. We included those patients who presented a suggestive anamnesis in combination with characteristic physical signs and, most of all, roentgenographic evidence and who remained under our observation, some until death. The evidence thus gained by an experienced observer can be convincing and even overwhelming. We may mention only the presence of a hemorrhagic pleural effusion, which is almost pathognomonic for malignant neoplasm. Not to consider such patients as having pulmonary neoplasm would be doing injustice to the possibilities of clinical and roentgenographic interpretation and would lead to serious consequences for patients who have no metastases and whose primary



Fig 1—Roentgenograms of a patient showing growth of a peripheral tumor without demonstrable atelectasis

growth is not accessible through the bronchoscope. We fully realize that the emphasis should be on the examining physician's special knowledge and experience with tumor of the lung. Since roentgenographic evidence is, next to tumor tissue itself, by far the outstanding diagnostic demonstration, we have illustrated the most characteristic features and some of the changes, indicating the periods of development (figs 1 to 4). The most essential factor in the development and the variability of this evidence is the degree of bronchial occlusion, if any, which is caused by the tumor. It determines the degree of secondary atelectasis and largely determines the degree of secondary abscess formation in the lung, which may dominate the roentgenogram. The bronchial occlusion can frequently be directly demonstrated by bronchography.

In the presentation of the results with roentgen therapy, we disclaim all technical knowledge of roentgenology. There is evidence, however, that experience and equipment, as they have been developed during the past decade or so, were progressively and skilfully applied to our patients by the roentgen specialists to whom they were referred for treatment. The dose ranged from about 1,200 to 16,000 roentgens. The wide range is explained by the increasing recognition of the inefficiency of weak irradiation. This tendency to increase the dose appears

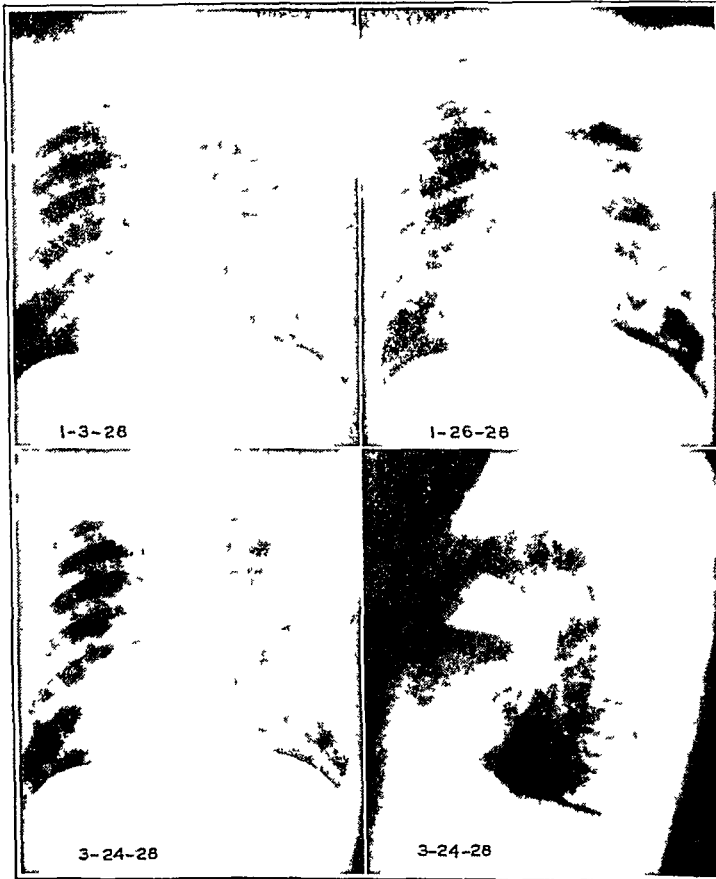


Fig 2—Roentgenograms of a patient showing development of wing-shaped atelectasis, with some interlobar pleuritis in the base of the right upper lobe, from carcinoma of a large secondary bronchus

in all reports, and the results obtained in our institution and elsewhere can be viewed on a fairly equal basis. Table 6 illustrates that in the various age groups the duration of life after the onset of symptoms in the patients who were treated was about the same as in the untreated patients. By comparison of the total groups, there is practically no difference. As a curative treatment, roentgen therapy was a complete failure, since the mortality was not diminished and the duration of life

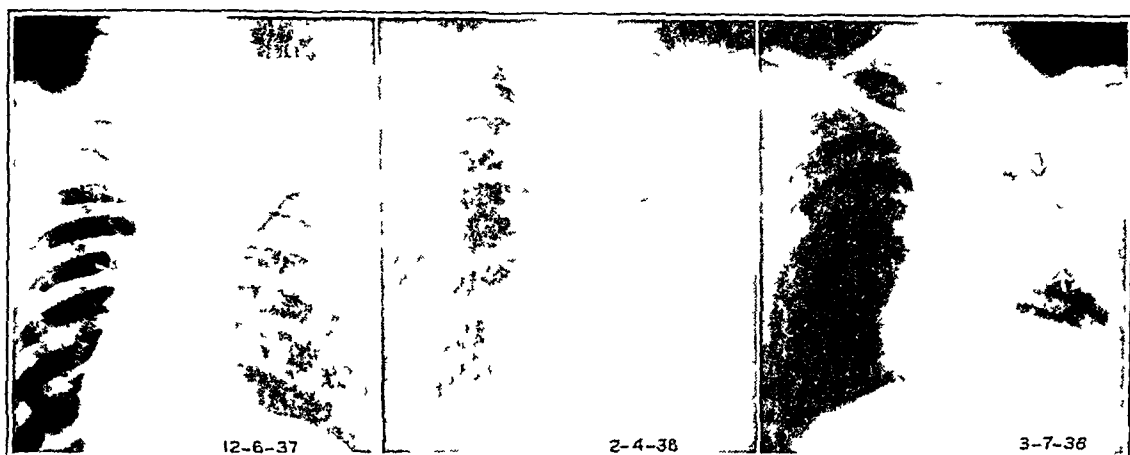


Fig 3—Roentgenograms of a patient showing, first, massive atelectasis from carcinoma of the main bronchus of the right upper lobe, second, obstruction of the bronchus of the middle lobe with residual atelectasis, and third, subsequent abscess formation there

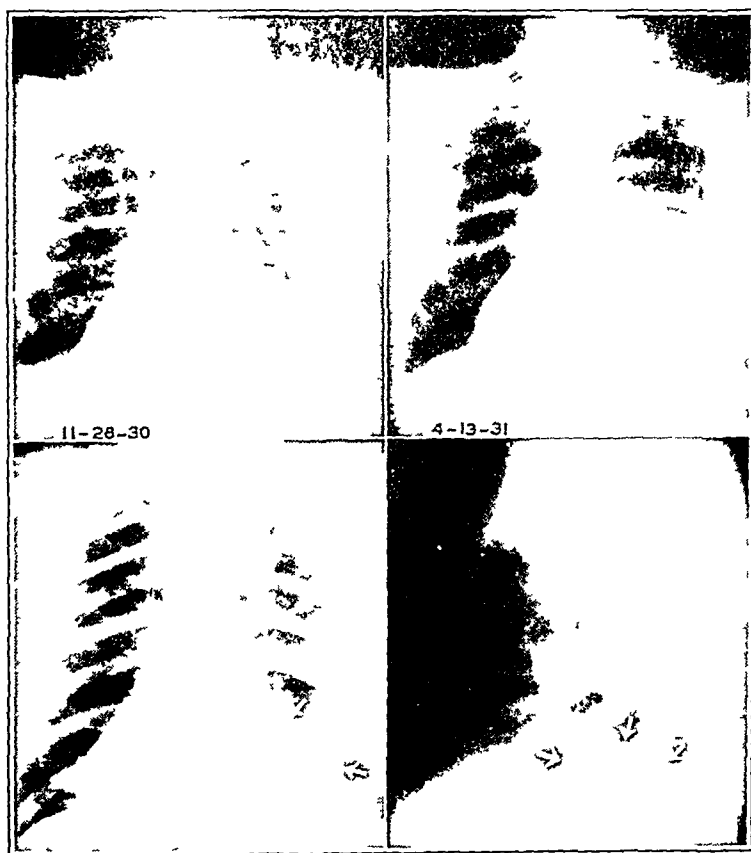


Fig 4—Roentgenograms of 2 patients, the upper two pictures showing atelectasis due to carcinoma of the bronchus of the right lower lobe resulting in abscess formation, and the lower two showing abscess formation within the tumor itself (frontal and lateral views), with no demonstrable atelectasis. Note the diffuse outline of the area in the upper films and the sharply circumscribed shadow of the tumor in the lower

not prolonged As Steiner³ pointed out in his paper, the destructive effect observed on histologic examination stayed much below what could be expected to annihilate the tumor, even when large doses had been given Clinically, there may be an effect in the form of some symptomatic relief which is caused by a release of bronchial occlusion and clearing of atelectasis following some shrinkage of the tumor Only 3 patients of our own group reported disappearance of symptoms How unjustified it is to relate mere symptomatic improvement to roentgen therapy is illustrated by the instance of a patient who had been seen at another clinic in our institution in November 1937 and on the basis of roentgenographic observations was advised to have roentgen therapy at home, away from Chicago When we recalled him for the purpose of this study in March 1939, he disclaimed all symptoms According to

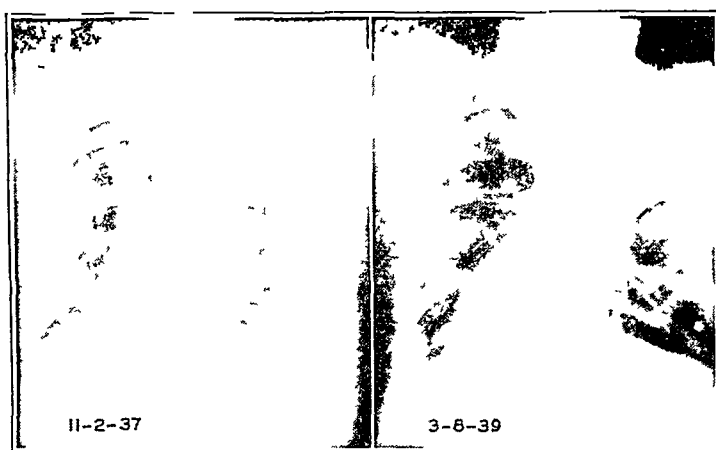


Fig 5—Roentgenograms of a patient showing unfavorable progress of untreated endobronchial carcinoma, accompanied by temporary gain in weight and symptomatic improvement

his information he had gained 35 pounds (15.9 Kg) from the lowest weight following the examination in 1937 Our own records showed a gain of 16 pounds (7.3 Kg) He asserted that, against advice, he had not taken irradiation or any other therapy Physical and roentgenographic examination of the chest revealed a considerable increase of evidence of carcinoma (fig 5) Bronchoscopic examination was then made, and a biopsy specimen taken from a friable tumor mass in the right upper bronchus showed a squamous cell carcinoma

Whatever roentgen changes can be observed also seem to be due to the clearing of atelectatic areas rather than to an essential destruction of the tumor We found such changes in only 2 patients, whose roent-

3 Steiner, P E Effects of Roentgen Therapy on Histologic Picture and on Survival in Cases of Primary Carcinoma of Lung, *Arch Int Med*, this issue, p 140

genograms are shown in figure 6. These patients, 1 of whom has previously been reported by Steiner and Francis⁴ as having a "superior pulmonary sulcus tumor," had been treated with 7,700 and 8,800 roentgens, respectively. How insignificant the effect on the tumor itself was can be judged by the fact that 1 of the patients died one week and the other, six weeks, after the films showing the clearing in the pulmonary field had been taken.

We cannot agree with the authors who maintain that extensive roentgen therapy should be attempted in any case, although it may not

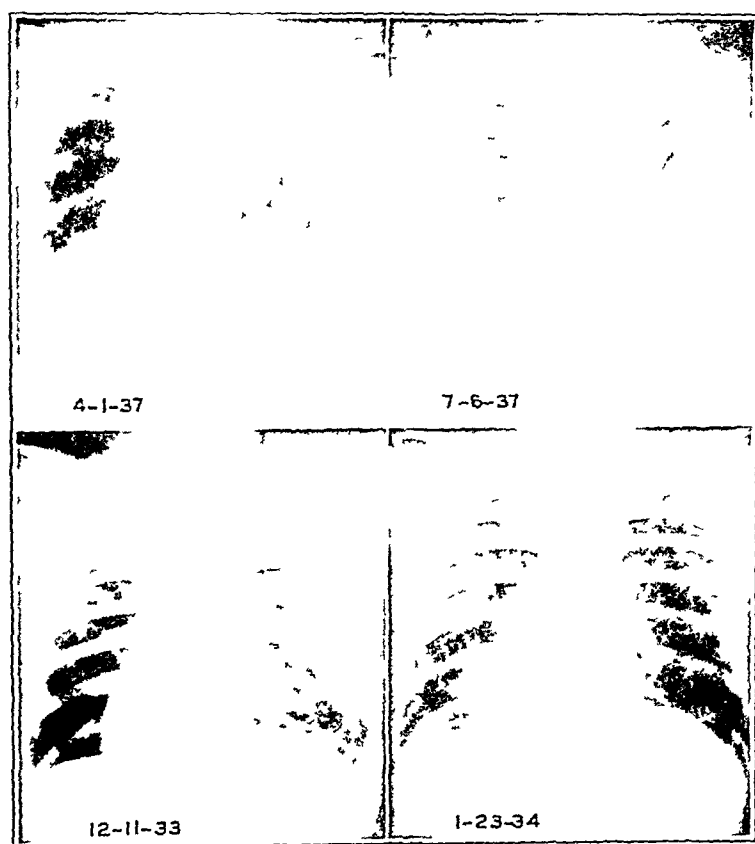


Fig 6—Roentgenograms of 2 patients showing clearing of atelectasis due to shrinkage of tumor following roentgen therapy.

hope to be curative since no serious ill effects occur. We found the effects from hard irradiation considerable—nausea, abdominal distress, severe headaches, general weakness and malaise being frequent and of considerable degree. The depleted blood stream has to be replenished by blood transfusions. The patient with hopeless pulmonary neoplasm dies an easier death without treatment, and the suggestion of roentgen therapy for psychologic reasons alone, it seems to us, is not in order.

⁴ Steiner, P. E., and Francis, B. F. Primary Apical Lung Carcinoma, *Am J Cancer* 22:776, 1934.

Our own search of the literature resulted in nearly the same experience as did Graham's. In most cases of reported cures, no serious proof of diagnosis is offered. In others, the evidence is insufficient. In spite of our contention that an acceptable diagnosis may be made by clinical and roentgenographic evidence only, i. e., a diagnosis sufficient for a plan of therapy, we would not undertake to report such patients as cured by any therapy without further diagnostic evidence. We have, however, no such patients, since of the 20 whom we included in that group, 15 have died, and the fate of 5 is unknown. There is reason to assume that the latter have died, too. This alone suggests the accuracy of the clinical and roentgenographic diagnosis.

The duration of life following the diagnosis may be considerable without any treatment (fig 5). Periods of survival of five years and more have been reported. Figure 7 shows a roentgenogram



Fig 7—Roentgenograms of a patient showing unchanged persistence of carcinoma for nearly four years, eventually resulting in fatal occlusion pneumonia.

of a patient whose condition remained unchanged for nearly four years. Autopsy after death from an occlusion pneumonia in the dependent lung lobe showed carcinoma. It is not likely that roentgen irradiation of 4,000 r, which is now considered as insufficient, caused the long survival, especially since the lesion appeared unchanged in films of the chest. Kernan,⁵ in discussion of the results of Vinson,^{6a} who reported survivals of four and a half to seven years after roentgen therapy, raised the question whether the long duration of life may not have been due to the peculiarities of some tumors which act as benign adenomas, although they are classified as carcinomas histologically,

5 Kernan, J. D. Carcinoma of the Lung and Bronchus. Treatment with Radium Implantations and Diathermy, *Arch Otolaryng* **17** 457 (April) 1933, in discussion on Vinson.^{6a}

6 Vinson, P. P. (a) Primary Malignant Disease of the Tracheobronchial Tree, *J. A. M. A.* **107** 258 (July 25) 1936, (b) Primary Carcinoma of the Bronchus, *Minnesota Med* **15** 15, 1932.

borderline cases between benign and malignant growth. In view of this, it is interesting that all of Vinson's⁶ and Vinson and Leddy's⁷ favorable results were obtained in patients with adenocarcinoma.

Our comments are not meant as a sweeping condemnation and discouragement of roentgen therapy. We simply wish to record our experience that up to the present irradiation has not been able to cure bronchogenic carcinoma. This is in much contrast to the beliefs of many. It may well be possible that in the future roentgen technic will be developed to a stage where the rays can reach these radioresistant growths with sufficient force.

At present the surgical removal of operable tumors must be the treatment of choice. During the past two years the first results obtained in our institution (Adams⁸) have been encouraging, and it is to be hoped that further improvement in surgical technic and postoperative care will be able to save a considerably higher number of patients in whom an early diagnosis is possible.

7 Vinson, P. P., and Leddy, E. T. Roentgen Treatment of Primary Malignant Disease of the Tracheobronchial Tree, *Ann. Otol., Rhin. & Laryng.* **41**: 1259, 1932.

8 Adams, W. E. Pneumonectomy for Bronchogenic Carcinoma of the Lung. Report of Successful Case Sixteen Months After Operation, *Illinois M. J.* **74**: 442, 1938.

PRIMARY TUMOR OF INFERIOR VENA CAVA, WITH CLINICAL FEATURES SUGGESTIVE OF CHIARI'S DISEASE

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AND

LAWRENCE BERMAN, M D

MINNEAPOLIS

Primary tumor of the vena cava inferior occurs rarely. This is indicated by the fact that in the examination of the records of 34,000 autopsies in the department of pathology of the University of Minnesota not a single report of its occurrence was encountered. Furthermore, a thorough search of the literature revealed the reports of only 4 cases.

The purpose of this paper is to report the occurrence of a leiomyosarcoma arising from and completely occluding the subdiaphragmatic portion of the inferior vena cava. The clinical and the postmortem observations in this case constitute the basis of the present study. From a diagnostic point of view the clinical picture was that of Chiari's disease (endophlebitis obliterans hepatica), except for certain vascular signs simulating those of constrictive pericarditis.

REPORT OF A CASE

L. S., a housewife aged 31, was admitted to the medical service of the University Hospitals on Oct 17, 1938. She had previously been seen in the outpatient department on Oct 4, 1938, at which time she complained of pain in the left side of the abdomen over a period of two years, cough of several months' duration and nausea and vomiting for two weeks. It was noted on October 4 that she had slight edema of the lower extremities as well as mild abdominal distention. On admission to the hospital her chief complaints were those of progressive enlargement of the abdomen and increasing edema of the lower extremities. The patient stated that in June 1938 a distressing cough developed after an acute infection of the upper respiratory tract. This cough persisted and at times was severe enough to be followed by vomiting. There was little expectoration, and the cough was always more severe at night. Palpitation and dyspnea on exertion had been noted since the birth of her last child, in June 1938. Aside from these symptoms, it appeared that the patient got along fairly well until four weeks prior to admission to the hospital. At that time she first noticed that her abdomen was enlarging, and shortly thereafter she began to have frequent attacks of nausea, occasionally

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From the Divisions of Internal Medicine and Pathology, the University of Minnesota Hospitals

with vomiting. These attacks had no apparent relation to the ingestion of food but were said to have been precipitated by slight activity. The abdomen enlarged progressively. Dyspnea, orthopnea and weakness developed. About ten days previous to her admission swelling of the ankles was noted.

The pain in the left side followed an injury to her left flank two years before. Since that time she had recurrent attacks of sharp pain in the left flank, occasionally radiating into the left groin and into the genital region. The pain was related to exertion.

Past and Family History—The patient had had bronchopneumonia and scarlet fever in childhood. The menstrual history was normal. Her husband was a chronic alcoholic addict and was confined to the state sanatorium for the insane. The father and mother of the patient as well as a brother and sister were living and well. No family history of cancer was elicited. The patient's 5 children were living and well, her last pregnancy had terminated normally in June 1938. There had been no miscarriages.

Physical Examination—The patient was a fairly well nourished young white woman, lying comfortably in bed. Her temperature was 97.5 F, and her pulse rate was 80. The head, eyes and mouth were normal on examination. The tonsils were present but not enlarged. Excursion of the diaphragm was limited by the distended abdomen. The pulmonary fields were clear, there were no signs of pleural effusion. The heart was not enlarged, the rate was regular and no murmurs were elicited. The heart tones were slightly diminished in intensity.

The abdomen was markedly distended. Shifting dullness was present, bulging in both flanks was noted, and a fluid wave was easily elicited. The superficial abdominal veins were slightly dilated. In the right upper quadrant a mass could be palpated which extended about 6 cm. below the costal margin in the mid-clavicular line. The mass was smooth and firm and was believed to be the liver.

Pelvic examination revealed a normal multiparous outlet and slight bilateral lacerations of the cervix. The internal genitalia could not be palpated accurately because of ascites. The rectum was normal. Marked pitting edema of both lower extremities was noted, with extension upward to involve the thighs. No edema of the upper extremities was noted. The radial pulse was small in volume, and on deep inspiration it became definitely diminished in amplitude (paradoxic pulse). The blood pressure was 128 systolic and 105 diastolic. The vital capacity was 2,500 cc (normal, 3,200 cc). Although the cervical veins were not noticeably distended, the venous pressure in the antecubital vein was recorded at 22.5 cm of blood by the direct method (fig 1). Because of increased venous pressure, ascites, edema, the absence of cardiac enlargement and the presence of pulsus paradoxus, a tentative diagnosis of constrictive pericarditis was advanced.

Laboratory Data—The specimen of urine taken on the patient's admission had a specific gravity of 1.024 and was acid in reaction, no albumin was noted. In the centrifuged sediment there were approximately 4 pus cells per high power field. Subsequent examinations revealed intermittent mild albuminuria. The phenolsulfonphthalein excretion in two hours was 51 per cent. The hemoglobin value on admission was 90 per cent (Sahli), the red blood count 4,500,000, and the white blood count 9,450, with 74 per cent neutrophils, 24 per cent lymphocytes and 2 per cent eosinophils. There were 2.5 per cent of reticulocytes. The content of urea nitrogen in the blood was 8.2 mg. per hundred cubic centimeters. Determination of the plasma protein showed albumin 2.3 per cent and globulin 2.1 per cent, the total being 4.6 per cent. The sedimentation rate was 14 mm the first hour and 40 mm the second hour (Westergren). The average red blood cell diameter

(Bock erythrocytometer) was 72 microns, the hematocrit reading was 49 per cent, the mean corpuscular volume was 85 cubic microns and the mean corpuscular hemoglobin value was 31 per cent. The icterus index was 9. The Wassermann test and the Mantoux test gave negative results. Roentgen studies showed the abdomen to be normal, and a retrograde pyelogram gave essentially negative results. The film of the heart taken at 6 feet (18 meters) showed the diaphragm markedly elevated because of the fluid in the abdomen. No definite pathologic condition could be seen in the lungs. The heart appeared to be within normal limits as to size and shape. Roentgen examination of the gastrointestinal tract gave negative results. The esophagus was normal. The electrocardiogram showed diminished amplitude of the QRS complex in all leads, with an isoelectric T wave in lead I, and diphasic T waves in leads II, III and IV.

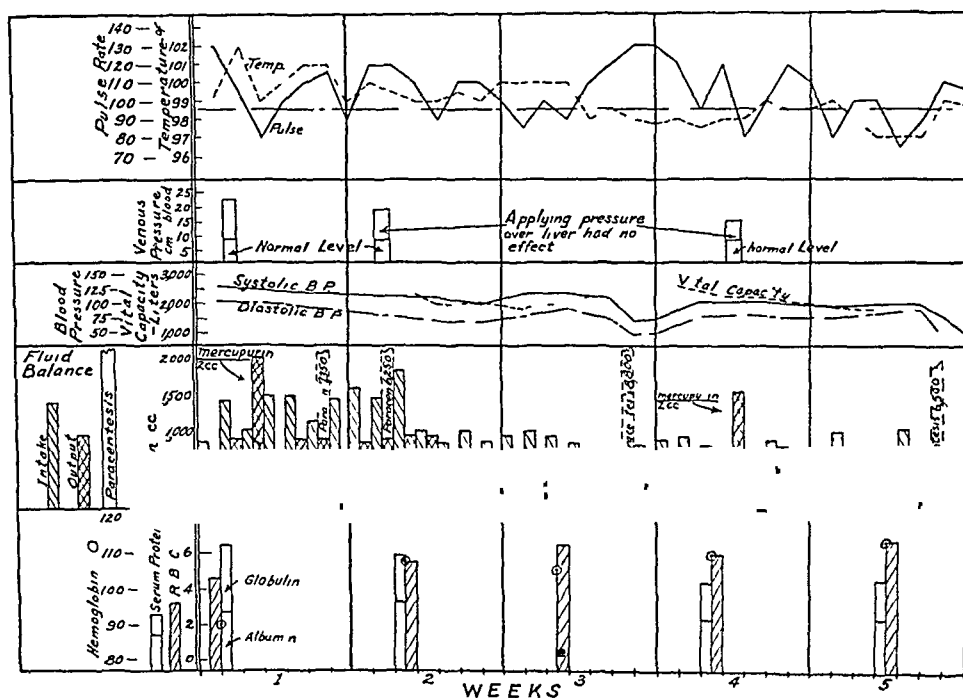


Fig 1—Chart showing important clinical features of occlusion of the inferior vena cava by a primary tumor (leiomyosarcoma). The pertinent features shown are the increased venous pressure in the upper extremities, the small pulse pressure, the reduced vital capacity, the decreased urinary output and the development of a secondary polycythemia.

Course—On October 18, 1938, 2 cc of mercupurin [a mercurin-theophylline preparation] (fig 1) was given intravenously with a resulting diuresis of 2,000 cc of urine. On October 22, 7,350 cc of straw-colored fluid was removed from the peritoneal cavity. The specific gravity of this fluid was 1.013, the cell count was 4,400 with 91 per cent monocytes and 9 per cent polymorphonuclear neutrophils, there were 15 Gm of protein per liter. No mucin was found. Examinations of the fluid for tumor cells and for tubercle bacilli gave negative results. On October 25, 6,250 cc of fluid was removed. After the removal of fluid, venous pressure, as recorded in the antecubital vein by the direct method, was 19 cm of blood (fig 1). No essential change in the blood pressure was noted. After paracentesis the liver was easily palpable and had a smooth, slightly tender surface. No other

abdominal masses were felt. The ascites rapidly reaccumulated. Studies were carried out to determine if there was any hepatic dysfunction. There was 30 per cent retention of bromsulphalein at the end of thirty minutes. The twenty-four hour specimen of urine contained 13 mg of urobilinogen (the upper limit of normal being 3.5 mg per day). The Takata-Ara test gave positive results, precipitation occurring in tubes 1, 2, 3, 4, 5 and 6. The levulose tolerance test gave positive results, the combined two hour rise being 134.

On October 23 fluoroscopic examination of the heart was carried out to determine whether the patient had constrictive pericarditis. No cardiac enlargement was noted, and all chambers showed good pulsations. There was no fixation of the heart. On October 26 kymographic studies showed fair amplitude of all cardiac pulsations. From these studies it was apparent that the patient did not have constrictive pericarditis. On October 31 it was noted that the superficial veins of the abdomen and of the lower portion of the chest were becoming more prominent. One of the collateral veins on the right side of the abdomen became thrombosed. The direction of the blood flow in the superficial veins of the abdomen was noted to be upward.

On October 28 the hemoglobin content had risen to 108 per cent. The red cell count was 5,750,000. The sedimentation rate showed no fall in the red blood cell count in the first hour and a fall of 2 mm in the second hour. Rapid accumulation of the ascites continued, hence, on November 6 it was again necessary to perform paracentesis, with a yield of 8,800 cc of straw-colored fluid. After this procedure the patient went into a state of shock, the pulse became thready and weak, and the blood pressure fell to 70 systolic and 50 diastolic. She recovered quickly from this, however.

On November 11 the venous pressure as estimated in the antecubital vein was found to be 16 cm of blood, and when pressure was applied over the hepatic region no change in the height of the venous pressure column was noted (fig 1). This obviously indicated that there was an obstruction to the outflow of blood from the liver into the inferior vena cava. Mercupurin was given at this time with only fair results.

Reexamination with the kymogram during phases of inspiration and expiration showed a typical paradoxical pulse. On expiration, however, there was good pulsation of both left and right sides of the heart, especially the left. The appearance was not at all suggestive of constrictive pericarditis. Marked pulsation of the diaphragm synchronous with that of the heart was present, especially on the right side. This could have indicated the presence of deep-seated diaphragmatic adhesions. The conclusion was that on the left side of the heart there were no adhesions of the pericardium. On the right side, however, some adhesions could have been present, but they were not demonstrable.

On November 15 the polycythemia had become more marked. At this time the hemoglobin content was 114 per cent and the red blood cell count 6,750,000, with 15,000 leukocytes. The hematocrit reading was 38.3 per cent. On this day the venous pressure in the antecubital vein was measured again and observed to be at the level previously noted (fig 1). Pressure on the liver again failed to influence the venous pressure. On November 19 paracentesis was carried out and 6,500 cc of reddish turbid fluid removed. Later in the same day the patient's condition became much worse, with appearance of extreme dyspnea and moderate cyanosis. The skin became cold, and the blood pressure was recorded at 98 systolic and 90 diastolic. The latter measurement was confirmed. The patient was placed in an oxygen tent, and external heat was applied. This treatment did not improve her condition. By the evening of November 19 the patient was in a moribund state.

The blood pressure could not be recorded. The pulse was irregular and thready. The respiratory rate dropped to 4, and breathing became extremely labored. The patient died shortly thereafter.

The outstanding features in the history were progressive weakness and dyspnea, attacks of nausea and vomiting, rapidly appearing edema of the lower extremities and abdominal distention for about four weeks prior to the patient's admission to the hospital. The pertinent clinical features were marked ascites, edema of the lower extremities extending up to the thighs, paradoxical pulse, small pulse pressure, enlarged liver and increased venous pressure in the upper extremities. The course of the disease was characterized by rapidly reaccumulating ascites. The total duration of the disease from the onset of obstructive symptoms to death was approximately twelve weeks. No doubt the tumor had been present for a considerable length of time before the onset of the symptoms, for the microscopic examination revealed a slow-growing tumor of low grade malignancy. The onset of the symptoms corresponded in all probability to that stage of obliteration of the inferior vena cava where the return flow of blood to the right auricle was being seriously impeded.

Pathologic Observations—Necropsy was performed by Dr. Berman eight hours after death. The body was that of a well developed and well nourished white woman, it measured 169 cm. in length and weighed about 145 pounds (65.8 Kg.). Jaundice was absent. There were severe posterior hypostasis, slight cyanosis of the nailbeds and marked pitting edema of both lower extremities to the level of the inguinal ligaments. The subcutaneous veins of the lower half of the thorax and the upper portion of the abdomen were apparent.

The peritoneal cavity contained 100 cc. of clear amber fluid. Numerous capillaries and small vessels transversed the entire parietal peritoneum. The edge of the liver was 13 cm. below the right costal margin in the midclavicular line. The diaphragm reached to the fourth rib on the right and the fifth rib on the left.

The right pleural cavity contained 1,200 cc. of opalescent amber fluid, the left was dry. There were no adhesions or scars on the surfaces of either lung. The pericardial sac was normal.

The heart weighed 260 Gm. There was no apparent hypertrophy or dilatation of any of the chambers and no lesions or deformities of the valves, septums or myocardium. There were no anomalies of the vessels of the neck or mediastinum. The coronary arteries were free of change. The superior vena cava and the right atrium were distended with blood, but there were no constrictions about any of the great vessels of the heart.

The inferior vena cava was obstructed by a tumor arising in the wall of the vessel. The tumor was 5 by 10 by 5 cm. (fig. 2). Its upper pole lay at a point a few millimeters inferior to the valve of the vena cava, its lower pole was 10 cm. inferior to the valve of the vena cava, and there was a blunt extension of the mass into the right hepatic vein for a distance of 4 cm. The lumen of the inferior vena cava below the mass was 3 mm. in diameter in the narrowest part because of the presence of thrombus, which extended down the vena cava into both common iliac veins. The thrombus extended into the left renal vein for 1 cm., but the renal vein was not completely occluded. The right ovarian vein contained canalized thrombus. The right renal vein and the left ovarian vein contained only fluid blood. A number of small veins in the broad ligament contained thrombi.

The spleen weighed 150 Gm. Trabeculae and corpuscles were apparent. There were no lesions in the esophagus, stomach, small intestine, appendix or colon. The pancreas, adrenal glands, kidneys, bladder and genitalia were normal grossly.

On the upper surface of the right lobe of the liver there was a slightly depressed dark red area connected by a narrow isthmus to a similar area in the lower third of the right lobe. On section, this was observed to be the external surface of deeply congested hepatic substance occupying the lateral half of the right lobe of the liver. The remainder of the liver was less severely congested. There were no lesions of the gallbladder or of the biliary ducts.

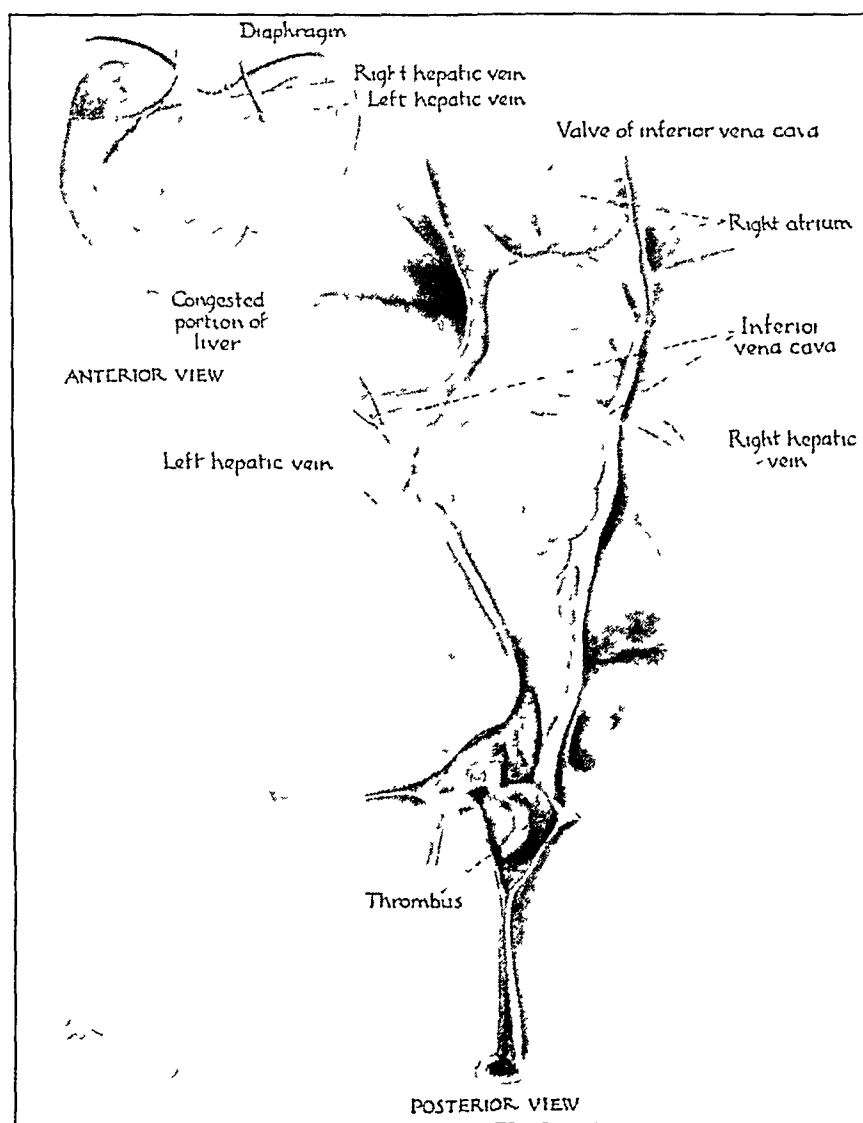


Fig 2—Drawing of the tumor (leiomyosarcoma) showing its origin and the extent of involvement of the inferior vena cava. The drawing in the upper left hand corner shows the extension of the tumor mass for a short distance into the right hepatic vein. As a result only the right lobe of the liver was severely congested.

The tumor in the inferior vena cava had a generally smooth surface grooved with many furrows, which divided the mass into a number of rounded elevations. The tissue had an opaque white color and a rubbery consistence. The wall of the inferior vena cava could be reflected from it with ease, except where it was attached laterally to the right side of the tumor. The vessel was thin, and it was applied

closely to the contours of the tumor. In a few places it was slightly adherent. There was a narrow slitlike passage between the tumor and the wall of the hepatic vein from the left lobe of the liver.

On section of the tumor there were seen numerous irregularly arranged filaments and whorls of tissue. The entire mass was solid and elastic, without any gross evidence of degeneration.

Microscopic sections revealed the tumor to consist of a network of spindle-shaped cells in longitudinal section enclosing bundles of cells in cross section. The cell bodies were long, some measuring 150 microns. Their cytoplasm was acidophilic and abundant, and their nuclei were long and rod shaped, with blunt rounded ends. The cells were generally uniform in size, except in the parts of the tumor showing more rapid and irregular growth. In such parts there were numerous cells with large and irregular, and sometimes multiple nuclei, some of

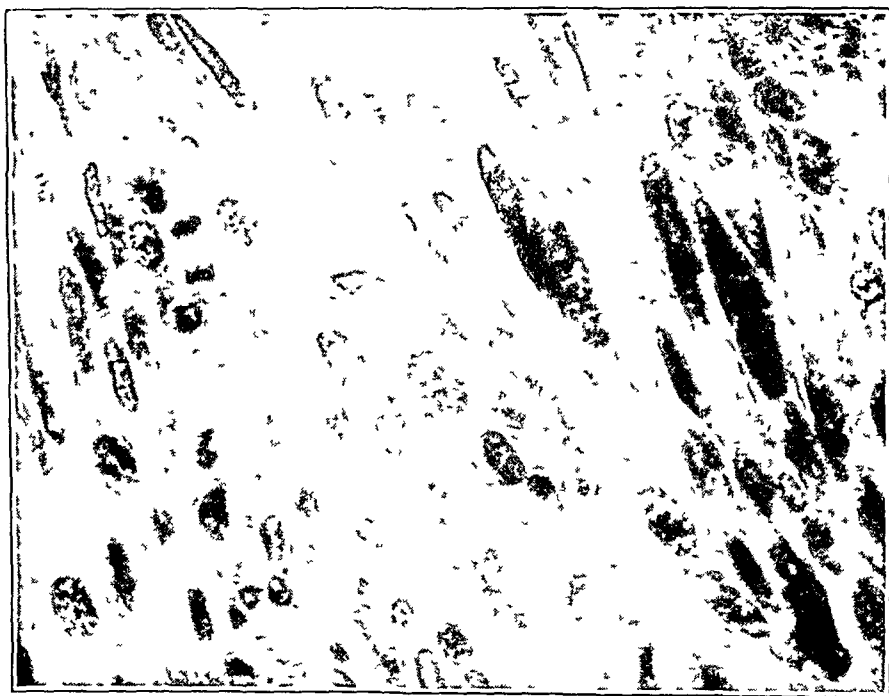


Fig 3—Photomicrograph of a section of the tumor of the inferior vena cava (leiomyosarcoma), $\times 560$. Note the abundant cytoplasm and the rod-shaped nuclei. A mitotic figure is present in the upper left corner.

which were undergoing mitosis (fig 3). Occasional areas of hyaline degeneration were encountered. The presence of collagenous fibrils between the cells was demonstrated by the use of connective tissue stains.

The morphologic structure of the cells and the architecture of the tumor were characteristic of smooth muscle cell tumors, and the occasional parts showing rapid and irregular growth revealed the sarcomatous character of the tumor. Therefore we considered it to be a leiomyosarcoma of low grade malignancy.

Sections from the liver revealed severe chronic passive congestion in the lateral half of the right lobe and less severe passive congestion of the remainder of the liver. The other viscera showed no significant histologic changes.

REVIEW OF THE LITERATURE

Perl¹ in 1871 reported the first case of primary tumor of the vena cava inferior. The patient was a 34 year old woman who complained of pain in the sacral region and lower part of the abdomen for nine months. Signs of obstruction appeared about six weeks before death. Edema of the ankles appeared, progressed and rapidly extended upward to the trunk. Dilated superficial veins appeared on the abdomen and thorax. Ascites developed, and a ballotable mass was present in the right upper quadrant. Because of the presence of casts in the urine and the development of oliguria, a diagnosis of chronic nephritis was made. Autopsy revealed marked ascites, and a retroperitoneal tumor was observed to arise in the inferior vena cava, expanding it to about the size of a fist. The tumor was located at a point just below the hepatic veins and extended into the renal veins. On the basis of the microscopic picture, Virchow made a diagnosis of myosarcoma.

The second case was reported by Unruh² in 1896. The patient was a 1 year old child with edema of the legs, which quickly progressed. There were no ascites, albuminuria and oliguria were observed. Rapid enlargement of the liver down to the midabdomen was noted. Jaundice did not appear. The veins of the lateral portions of the abdomen became noticeable, and anasarca developed. The pulse was rapid. Because of dyspnea and signs of compression of the left lung and widening of the cardiac borders, a diagnosis of pericardial effusion was made. The duration of symptoms of caval obstruction was about six weeks. Autopsy revealed enormous edema of the lower extremities, and 100 cc of ascitic fluid and 300 cc of pericardial fluid were found. The heart itself was normal. A hard white nodular tumor was found to occupy the inferior vena cava, extending from the hepatic veins for several centimeters into the right auricle. The hepatic veins were filled with thrombi, as was the portion of the inferior vena cava below the tumor. The portal vein was normal. Microscopic examination of the tumor revealed it to be endothelioma.

The third case was reported by Melchior³ in 1928. The patient was a woman 24 years of age. The chief complaints were of intermittent pain in the sacral region for two years. She was treated for sciatica. Later she complained of a sense of fulness in the abdomen, accompanied

1 Perl, L. Ein Fall von Sarkom der Vena cava inferior, Virchows Arch f path Anat **53** 378, 1871

2 Unruh, F. In vivo diagnostizierte Thrombose der Vena cava inferior verursacht durch ein Endotheliom der Wand bei einem einjährigen Kinde, Deutsche med Wchnschr **22** 746, 1896

3 Melchior, E. Sarkom der Vena cava inferior, Deutsche Ztschr f Chir **213** 135, 1928

by occasional vomiting. A tumor as large as a fist was palpable in the right upper quadrant. The colon appeared to lie over this mass. A diagnosis of an inflammatory cyst of the pancreas was first considered, and an exploratory operation was done. A tumor was removed which was observed to be a portion of the inferior vena cava. The diagnosis of the specimen was fibrosarcoma of the inferior vena cava. The patient died subsequently of gangrene of the lung. Permission for autopsy was not obtained.

The fourth case was reported by König⁴ in 1931, the patient being a 29 year old woman. In 1929 a sarcoma of the ovary was removed. In 1930 a distinct mass appeared in the right upper quadrant. The tumor was nontender, lay deep in the abdomen and was diagnosed as a retroperitoneal sarcoma. An exploratory operation was performed, and a tumor 6 cm long, well encapsulated and occupying the inferior vena cava was removed. Microscopic examination showed it to be a round cell sarcoma. Ten months after the operation the patient was still in excellent condition. However, whether the tumor removed from the inferior vena cava was primary or secondary to the ovarian sarcoma was not definitely determined.

DIFFERENTIAL DIAGNOSIS AND PATHOLOGIC PHYSIOLOGY

Constrictive Pericarditis—From a consideration of the clinical and the laboratory data in the case reported here, various diagnostic possibilities were considered. As previously stated, constrictive pericarditis appeared at first sight as the most logical diagnosis. This was suggested by rapidly recurring ascites, paradoxical pulse, small pulse pressure, increased venous pressure in the upper extremities and edema of the lower extremities. The electrocardiographic changes of low voltage also supported this view. The diagnosis, however, had to be discarded when fluoroscopic examination of the heart revealed normal pulsation of all chambers, a feature which is invariably absent in chronic cardiac compression due to pericardial disease. The kymographic studies showing the normal amplitude of pulsations of all chambers and great vessels of the heart substantiated the absence of any constrictive phenomena.

Portal Cirrhosis—Because of definite evidence of dysfunction of the liver as indicated by hepatic function tests, a diagnosis of portal cirrhosis was considered. However, features of cirrhosis, such as nodular liver, jaundice, splenomegaly, macrocytic anemia and spider angiomas, were not present. The large smooth liver and the presence of urobilinogenuria were explained more readily on the basis of chronic passive congestion. This was likewise thought to explain the transitory albuminuria.

⁴ König, E. Sarkome der Vena cava inferior, *Chirurg* 3 104, 1931

Furthermore, the vascular signs noted in this case have not been described in cases of cirrhosis of the liver

Chiari's Disease—Obliterating endophlebitis of the hepatic veins, Chiari's disease,⁵ has similar features in many respects to those in the present case. Chiari's disease, so far as can be determined, has never been diagnosed during life, being usually mistaken for cirrhosis of the liver. Briefly, the clinical picture⁶ is one of gradual onset over a period of several months, with the development of marked ascites which accumulates rapidly after removal. The liver is enlarged. The spleen may be enlarged, and there may be slight jaundice. Albuminuria has been noted at times and probably indicates secondary obstruction of the vena cava. Gastrointestinal symptoms are marked, and a superficial collateral circulation indistinguishable from that seen in cirrhosis is present.

Thrombosis of the hepatic veins may occur as a rare complication of polycythaemia vera.⁷ However, the fact that the signs of polycythemia were not present at the onset of the disease ruled against a diagnosis of polycythaemia vera in our case. The polycythemia which gradually appeared was in all probability due to hemoconcentration above the diaphragm. Had studies been carried out on blood removed from a vein of the lower extremity, it might have been possible to clarify this question.

There are many other causes of obliteration of the vena cava inferior which must be considered in a differential diagnosis, such as thrombosis arising in the vena cava itself as a result of infectious diseases or by extension from localized foci of diseases, as in puerperal sepsis or diseases of the liver. Obstruction of the vena cava may be caused by new growths which may either invade the vena cava or cause external pressure from without, such as tumors, gummas, enlarged peritoneal glands, pancreatic cysts or hepatic abscesses. Congenital obliteration of the vena cava inferior is also a rare possibility.

While it may be often impossible to determine the etiologic factor which is responsible for caval obstruction, it may be possible to determine the level at which the obstruction occurs. For the purpose of differential diagnosis the vena cava may be divided roughly into three anatomic divisions: the upper third, that portion of the vena cava which extends from the entrance of the hepatic veins to the right auricle (sub-

5 Chiari, H. Ueber die selbstständige Endophlebitis obliterans der Hauptstämme der Venae hepaticae als Todesursache, Beitr z path Anat u z allg Path **26** 1, 1899.

6 Eppinger, H. Die Leberkrankheiten. Berlin: Julius Springer, 1937, p. 469.

7 Solval, A. R. Hepatic Complications in Polycythaemia Vera, Arch Int Med **62** 925 (Dec) 1938.

diaphragmatic portion), the middle third, that section extending from below the opening of the hepatic veins to the renal veins, and the lower third, that section extending from below the entrance of the renal veins to the bifurcation into the common iliac veins

The following physical features are listed according to the level of obstruction

1 Lower Third

- (a) Absence of edema of lower extremities, unless involvement of either one or both common iliac veins is present
- (b) Superficial collateral circulation, manifested by development of superficial veins in groins and over lower part of abdomen and flanks
- (c) Absence of albuminuria

2 Middle Third

- (a) Edema of lower extremities, followed by development of a superficial collateral circulation (occurs in practically all cases of gradual occlusion)
- (b) Albuminuria as a rule
- (c) Occasional presence of edema of abdominal wall

3 Upper Third (subdiaphragmatic obstruction)

- (a) Ascites
- (b) Edema of lower extremities
- (c) Enlargement of liver
- (d) Albuminuria
- (e) Development of superficial collateral circulation

The following signs are added to high caval obstruction from the observations made in the study of this case

- (f) Paradoxical pulse
- (g) Low pulse pressure
- (h) Electrocardiographic changes
- (i) Increased venous pressure in upper extremities and failure to raise venous pressure in upper extremities when pressure is applied over liver

An exceptional feature was the presence of increased venous pressure in the upper extremities (fig 1) While no measurements of venous pressure could be made in the lower extremities because of the massive edema, it was reasonable to assume that the venous pressure was abnormally elevated and that this increased pressure was transmitted upward along the collateral circulation to the tributaries of the superior vena cava. Hence, it would appear that the return of an abnormal volume of blood to the heart through the superior vena cava by way of the collateral circulation could have produced a certain amount of engorgement of some of the principal veins emptying into it. Presumably this engorgement would be reflected as increased venous pressure in the antecubital veins, the point at which the venous pressure determinations were made

This is not at all impossible to comprehend when it is remembered that the superior vena cava is normally adapted to carry only about a third of the venous blood returned to the right atrium. With closure of the inferior vena cava this quantity is much increased, and from the

point of view of dynamics it seems likely that the superior vena cava cannot carry the larger amounts of blood without elevation of pressure in the tributary veins

The paradoxical pulse was one of the most striking features in this case, and its presence strongly suggested the diagnosis of compression of the heart. As yet the mechanism of the production of the intrinsic variety of paradoxical pulse has not been elucidated clearly, although many theories have been advanced for its explanation. However, certain conditions must operate to bring it about. There must occur a marked reduction at the end of inspiration in the stroke output of the heart which is responsible for a diminution in the amplitude of the radial pulse. The reduced stroke output is a consequence of the failure of the right or left auricle to fill adequately during the inspiratory phase. We can only speculate as to the mechanism that produced the paradoxical pulse in this case. It is believed that the chief collateral circulation from the inferior vena cava occurred by way of the lumbar veins to the ascending lumbar veins, which in turn drained into the azygos vein and thence into the superior vena cava. Anatomically, the azygos vein at its termination arches over the root of the right lung before it makes its entrance into the superior vena cava. Thus it lies in direct proximity to the medial surface of the right lung. If we assume that the azygos vein is abnormally dilated because of increased blood flow through it, then on deep inspiration the pressure exerted on its wall by the inflating lung would tend to compress it so as to cut down the flow of blood into the superior vena cava. Obviously the downward expansion of the lung in the present case was limited by the high diaphragm, and the greatest expansion would occur in a transverse direction. On deflation of the lungs, compression of the azygos vein would tend to be removed.

The electrocardiographic changes are best explained by a reduced flow of blood into the heart, the coronary flow being simultaneously reduced, thus a state of coronary insufficiency develops similar to the condition that obtains in constrictive pericarditis.

SUMMARY

A case of occlusion of the subdiaphragmatic portion of the inferior vena cava by a leiomyosarcoma is reported. The literature of occlusion of the vena cava inferior by primary tumors is reviewed.

The presence of paradoxical pulse and of high venous pressure in the upper extremities were clinical features which complicated the differential diagnosis. The possible mechanisms by which these phenomena were produced are discussed.

Similarity to Chiari's disease, obliterating endophlebitis of the hepatic veins, was noted in the present case. Clinical features are discussed which may serve to distinguish the two conditions in the future.

DIAGNOSTIC SIGNIFICANCE OF DETERMINATIONS OF SERUM LIPASE

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AND

H L BOCKUS, M D

PHILADELPHIA

A review of recent experimental and clinical data suggests that determinations of serum lipase may be of value in the diagnosis of diseases of the pancreas. The reports in the literature are limited largely to application of the test to groups of selected patients with pancreatic and hepatic diseases. This report is concerned with an analysis of the results of this test on a wide variety of clinical material over a period of three years. It was thought that this type of study might throw some light on the degree of specificity of the test for pancreatic disease and might possibly help to clarify the relation between hepatic dysfunction and hyperlipasemia.

METHOD

We used a modification of the Loevenhart method, as suggested by Cherry and Crandall¹. Basically, the method depends on the estimation of fatty acid produced by the hydrolysis of an olive oil emulsion on which the lipase in the blood serum has been acting during a twenty-four hour period under optimum conditions of p_H and temperature. The determination of serum lipase is carried out in the following manner:

- 1 Place 3 cc of distilled water in each of two test tubes, *A* and *B*
- 2 Add 1 cc of serum to each tube and shake
- 3 Place tube *A* in a water bath at 100 C for five minutes to inactivate the lipase. Tube *A* is the control tube. Be sure to cool tube *A* before proceeding to step 4
- 4 Add 0.5 cc of buffer solution to each tube. (Prepare the solution as follows: Mix 10 cc of a one-third molar solution of disodium hydrogen phosphate [Na_2HPO_4] and 3 cc of a one-third molar solution of potassium dihydrogen phosphate [KH_2PO_4].)
- 5 Add 2 cc of a 50 per cent olive oil emulsion to each tube and shake. (The substrate was prepared by the Abbott Laboratories, list 8100, with 5 per

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1 Cherry, I S, and Crandall, L A. The Specificity of Pancreatic Lipase. Its Appearance in the Blood After Pancreatic Injury, *Am J Physiol* **100** 266 (April) 1932. In the interpretation of studies of serum lipase reported prior to 1932, it is essential to determine what substrate was employed. At that time Cherry and Crandall showed that true lipase, which splits olive oil, differs from esterase, which acts on simple esters such as ethyl butyrate or tributyrin.

cent solution of acacia, as the emulsifying agent, to which 0.2 per cent of sodium benzoate had been added as a preservative)

6 Incubate for twenty-four hours at 37.5 C

7 Add 3 cc of 95 per cent alcohol and 2 drops of a 1 per cent solution of phenolphthalein

8 Titrate each tube to a faint pink, using a twentieth-normal solution of sodium hydroxide

9 Subtract the value for control *A* from that for specimen *B*

10 Results are thus expressed in terms of cubic centimeters of a twentieth-normal solution of sodium hydroxide

Previous observers have not agreed on a figure for serum lipase which can be accepted as the upper limit of normal. From the point of view of quantitative chemistry, the test is somewhat short of the ideal. Different batches of olive oil emulsion show slight variations in the amount of titratable acidity in the control specimens, probably referable to varying amounts of free fatty acids in the substrate. It is possible that different batches of olive oil emulsion may vary as to the ease with which the olive oil may be broken down by the serum lipase. The composition of an olive oil emulsion at different periods after its preparation offers a variable which is difficult to evaluate. An attempt to measure accurately 2 cc of a heavy olive oil emulsion offers in itself a sizeable variant in individual instances. However, values for duplicate determinations on the same specimens, particularly those of higher lipase content, have been surprisingly close.

Comfort² stated that significant values are in excess of 1.5 cc of twentieth-normal solution of sodium hydroxide. An analysis of our preliminary determinations indicated that some importance might be attached to any figure above 1.0 cc. Temporarily, for our series, we are accepting the latter figure as the maximum normal. However, the most significant figures occur in the higher brackets. Our highest value, 5.5 cc, is somewhat lower than the highest value reported by Comfort³. We are unable to account for our inability to obtain by titration values in excess of approximately 5.0 cc in cases of acute pancreatitis. However, for experimentally induced acute pancreatitis in dogs Baxter, Baxter and McIntosh⁴ reported values ranging from 3.0 to 5.5 cc, values not dissimilar to our maximum figures for acute pancreatitis.

The serum lipase is said to be maintained at normal levels for at least two weeks after operation in pancreatectomized dogs, from which

2 Comfort, M. Serum Lipase Its Diagnostic Value, Proc Staff Meet, Mayo Clin 10 810 (Dec 18) 1935

3 Comfort, M. Serum Lipase Its Diagnostic Value, Am J Digest Dis & Nutrition 3 817 (Jan) 1937

4 Baxter, H., Baxter, S. G., and McIntosh, J. F. Variations in the Level of Serum Lipase in Experimental Pancreatitis, Am J Digest Dis & Nutrition 5 423 (Sept) 1938

one would infer that a functioning pancreas is not essential for the maintenance of a normal level. There is some experimental work supporting the theory that the source of the normally circulating serum lipase is not the pancreas but is possibly the liver or muscles, or both. According to that theory, serum lipase of pancreatic origin enters the blood stream only after trauma to the pancreas or after obstruction of the pancreatic ducts. The validity of the hypothesis is not above question (case 400).

ANALYSIS OF VALUES FOR SERUM LIPASE IN 371 CASES

Determinations were carried out in 371 cases during the course of this study, from November 1935 to November 1938. Determinations in approximately 75 additional cases were excluded because of lack of sufficient clinical data. All of the determinations were carried out by one or the other of two persons, to minimize the personal equation in the

TABLE 1—*Range of Abnormal Serum Lipase Values*

Serum Lipase, in Cc N/20 NaOH	Number of Determinations
1.01 to 1.50	38
1.51 to 2.00	16
2.01 to 2.50	16
2.51 to 3.00	2
3.01 to 3.50	6
3.51 to 4.00	2
4.01 to 4.50	3
4.51 to 5.00	1
5.01 to 5.50	2
Total	86

interpretation of results. In some instances many tests were performed in the same case during the course of the illness. Six hundred and sixteen separate determinations, not including duplicate tests on the same day, were made during the period. All values in excess of 1.0 cc were considered abnormal. In 50 cases (13.5 per cent) there were readings above that level. Eighty-six separate determinations (14 per cent) were above 1.0 cc. The number of determinations within the abnormal range may be seen in table 1.

Acute Pancreatitis—Forty separate determinations of serum lipase were carried out in 11 cases of acute pancreatitis. In 9 cases the values were high at some time during the course of the illness. Normal values were obtained in 2 cases. In case 78 the presence of acute pancreatitis was probable, but the diagnosis was not absolutely established. In case 439 the first lipase determination was made two weeks before the condition was found at operation, and the second test was carried out one week after operation. The case reports follow.

CASE 35—The value for lipase was 4.0 cc. The diagnosis of acute pancreatitis was made clinically, recovery took place without operation.

CASE 51—Acute hemorrhagic necrosis of the pancreas was found at operation, the pancreas was incised from head to tail. Preoperatively the values for lipase were 22 and 0.8 cc. Immediately after operation the value was 3.1 cc, and eight months after recovery it was 0.26 cc.

CASE 78—The findings at operation were atypical fatty necrosis of omentum in the region of the pancreas, unidentified necrotic material in the lesser peritoneal sac, and cholelithiasis. Recovery took place. The lipase values were 0.2, 0.5, 0.16, 0.26 and 0.52 cc.

CASE 106—The lipase value was 2.5 cc. The diagnosis was clinical only, recovery took place without operation.

CASE 131—G. C., a white man, was admitted to the hospital on Sept. 25, 1937, with jaundice of three weeks' duration and with a history of intermittent attacks of epigastric pain. There was no visualization of the gallbladder by intravenous cholecystography. The value for serum bilirubin was 6 mg. per hundred cubic centimeters. The bromsulphalein retention (dose, 2 mg. per kilogram of body weight) was 60 per cent. The value for serum lipase was 1.2 cc. On October 9 the jaundice had receded (bilirubin, 3 mg.), the bromsulphalein retention was 45 per cent. The lipase values were 0.94 cc. on October 2 and 0.46 cc. on October 9. Exploratory operation on October 10 revealed a sizable soft mass which involved the head of the pancreas. Cholecystostomy was performed. Hyperbilirubinemia and excessive retention of dye were no longer noted. There was a recurrence of pain on November 10 with reopening of the biliary fistula. The value for serum lipase was 0.96 cc. on November 9 and 0.78 cc. on November 16. The fistula was closed, there was an uneventful convalescence to November 24, at which time the patient was discharged. Follow-up study showed lipase values of 2.8 cc. on November 30, 1.8 cc. on December 4 and 0.18 cc. on April 19, 1938. Observation was continued to March 1939, at which time the patient was admitted for standardization for diabetes which had developed apparently as a result of the pancreatic inflammation. The lipase values at the time were 0.8 and 0.42 cc.

CASE 192—Acute hemorrhagic pancreatitis was found at operation. The lipase value was 1.68 cc. four days after operation, recovery took place.

CASE 302—A white woman 38 years of age was admitted to the hospital for study on April 2, 1938, because of attacks of biliary colic since her pregnancy in June 1937. The level of serum bilirubin was normal, and the lipase value was 0.74 cc. While under observation the patient had an attack of severe pain in the upper abdominal region, accompanied by slight fever without leukocytosis and followed by jaundice. On April 21, three days after the attack, the value for serum bilirubin was 6 mg. per hundred cubic centimeters and that for lipase was 1.86 cc. The values for lipase on April 24 and on April 25 were 1.38 and 1.34 cc. Operation was deferred until April 25, several days after subsidence of the attack and the jaundice. The gallbladder, filled with stones, was removed. The common duct and the head of the pancreas were thought to be slightly larger than normal but of normal consistency. The duct was not probed. Recovery was uneventful. On May 8 the values for serum bilirubin and for lipase (0.80 cc.) were normal. It is probable that the elevation of the value for lipase had been due to an acute transient pancreatitis.

CASE 400—A white woman aged 48 was admitted to a colleague's service with acute pain in the upper abdominal region which radiated to the back, nausea, vomiting, a leukocyte count of 20,000, with 84 per cent neutrophils, and a fasting blood sugar of 366 mg. per hundred cubic centimeters. There was no jaundice. After three days the value for serum lipase was 4.18 cc. Death occurred on the

eleventh day, at which time the serum lipase was 0.06 cc. Autopsy revealed a severe hemorrhagic necrosis of practically the entire pancreas. The almost complete disappearance of lipase from the blood stream is of interest in view of the lack of any appreciably functioning pancreatic tissue at necropsy.

CASE 373—A woman 55 years of age complained of repeated attacks of epigastric pain radiating to the back, of five months' duration. Cholecystectomy had been performed many years previously, there was a recurrence of pain the day before admission on June 7, 1938. The value for serum bilirubin was 4 mg., and the lipase value was 3.32 cc. By June 14 the attack had subsided, and the lipase level was 2.36 cc. Pain recurred on July 1. The next day the lipase level was 5.2 cc., and the serum bilirubin mounted to 2.6 mg. The patient remained symptom free thereafter, an exploratory operation was not done because she had severe myocardial degeneration with auricular fibrillation. The presumptive diagnosis was recurrent subacute pancreatitis, possibly associated with stone in the common duct.

CASE 439—This patient had cholelithiasis, with slight jaundice. The serum lipase level on admission was 0.04 cc. At operation, two weeks later, areas of pancreatic necrosis were noted, in addition to gallstones. There had been nothing in the clinical course to suggest pancreatitis. Convalescence was uneventful. The lipase value one week after operation was again normal, 0.12 cc.

CASE 444—A woman 47 years of age was admitted to the hospital on Dec 31, 1938, in an attack of biliary colic with chills and fever. There was no hyperbilirubinemia, but the sugar tolerance was decreased. On Jan 2, 1939, the value for serum lipase was 2.34 cc., on January 4, 1.86 cc., on January 5, 2.14 cc., and on January 10, 1.18 cc. Operation on January 12 revealed a thickened gallbladder, filled with stones, grossly, the common duct and pancreas appeared to be normal. Cholecystectomy was performed. Lipase values on January 21 and April 2 were 0.90 and 0.40 cc., respectively. We assumed that some inflammation of the pancreas, concomitant with the cholelithiasis, had subsided to a great extent before operation.

Comment—There is ample clinical and experimental evidence that the amount of lipase in the serum is frequently increased in acute pancreatitis. This increase has been accredited to two possible mechanisms: (1) absorption of lipase directly into the blood stream from necrotic pancreatic tissue and (2) absorption of lipase from the smaller pancreatic ducts which have been blocked by edema secondary to adjacent inflammation. In various studies of serum amylase in acute pancreatitis, Gray⁵ and his co-workers stated the belief that increases in the amount of this enzyme did not parallel increases in the severity of the disease. Our series is too small to justify similar comment on serum lipase. Gray⁵ and his associates mentioned the occurrence of a transient rise of the level of serum amylase in cases of mild acute pancreatitis, the level returning to normal, in some instances, within a few hours. The possibility of a similar transient rise in lipase may be

⁵ Gray, S. H., Probst, J. G., and Heifetz, C. J. Transient Acute Pancreatitis, *Ann Surg* **108** 1029 (Dec) 1938. Probst, J. G., Wheeler, P. A., and Gray, S. H. Perforated Peptic Ulcer. Its Differentiation from Acute Pancreatitis by Blood Diastase Determinations, *J Lab & Clin Med* **24** 449 (Feb) 1939.

considered in the interpretation of values obtained several days after the onset of the acute attack

In experiments with dogs, Cherry and Crandall¹ found a secondary rise in serum lipase after ligation of the pancreatic duct. A similar rise occurred in case 51 after incision of the pancreas. In case 400, in which autopsy demonstrated an almost complete necrosis of the pancreas, there was a drop from an initial level of 4.18 cc., eight days before death, to 0.06 cc., a few hours before death. Such a drop might be explained on the basis of pancreatic exhaustion. It is apparent that acute pancreatic inflammation may not always be associated with an elevation in the serum lipase. Comfoit reported an instance of that type, and our case 78 falls into the same group. Nevertheless, it is not possible to scan the figures in our cases of acute pancreatitis without concluding that studies of the enzymes in the serum are of tremendous assistance in the diagnosis of acute inflammation of the pancreas. The determination of serum lipase loses some of its clinical value because of the twenty-four hour incubation period which is necessary for the performance of the test by the technic described. The determination of the serum amylase would seem to be of greater clinical value in the cases of acute pancreatitis because of the rapidity with which that test can be performed, either by the copper-reduction method⁶ or by viscometric methods,⁷ which require only one hour.

Carcinoma of the Pancreas—Twenty serum lipase determinations are recorded for 8 cases of carcinoma of the pancreas. Values above 1 cc. were obtained in 5 of them (62.7 per cent). Only cases in which the diagnosis was confirmed by operation or necropsy were considered. The case reports follow.

CASE 23—The patient suffered from obstructive jaundice and diabetes. At operation cancer of the head of the pancreas was discovered, cholecystogastrostomy was performed. Two lipase determinations were below 0.2 cc.

CASE 36—One test for lipase gave a value of 0.9 cc. There was obstructive jaundice, operation confirmed the diagnosis, a cholecystojejunostomy was done.

CASE 54—The one lipase value determined was 0.8 cc. The operation confirmed the diagnosis of carcinoma of the head of the pancreas with biliary obstruction. The patient died, no necropsy was performed.

⁶ Somogyi, M. Studies on Blood Diastase, *Proc Soc Exper Biol & Med* 29 1126 (June) 1932.

⁷ Davison, W. C. Viscometric Method for Quantitative Determination of Amylase, *Bull Johns Hopkins Hosp* 37 281, 1925. Elman, R., Arneson, N., and Graham, E. A. Value of Blood Amylase Estimation in Diagnosis of Pancreatic Disease, *Arch Surg* 19 943 (Dec) 1929. Elman, R., and McCaughan, J. M. Quantitative Determination of Blood Amylase with Viscosimeter, *Arch Int Med* 40 58 (July) 1927. McCaughan, J. M. Value of Estimations of Blood Amylase in the Diagnosis of Suspected Pancreatic Disease, *Surg, Gynec & Obst* 59 598 (Oct) 1934.

CASE 56—Values for lipase were 0.2 and 1.4 cc. Necropsy revealed a carcinoma involving the pancreas, duodenum and ampulla of Vater, with obstruction of the common duct.

CASE 96—Two tests for lipase gave values of 1.3 and 1.1 cc. Carcinoma of the head of the pancreas, with jaundice, was present. Cholecystojejunostomy was done, autopsy was performed.

CASE 97—Values obtained in three tests for lipase were as follows: 0.6, 1.1 and 0.1 cc. Carcinoma of the pancreas was present. Cholecystojejunostomy was done.

CASE 259—The following values were obtained in ten tests for lipase: 5.04, 4.8, 4.2, 4.2, 3.8, 3.5, 2.4, 2.1, 1.9 and 0.48 cc. The patient was jaundiced. There was surgical confirmation of the diagnosis of carcinoma of the head of the pancreas. Cholecystojejunostomy was performed. The progressive drop in values for lipase, which occurred over a period of eleven weeks, is noteworthy. The first two tests were done preoperatively and the last test was done shortly before the patient's death.

CASE 453—Two tests gave values for lipase of 2.2 and 1.72 cc. At the first operation the condition was thought to be acute pancreatitis, but subsequent operation showed a nodular malignant growth in the pancreas.

Comment—Carcinoma of the pancreas gave rise to increased values for serum lipase in 62.7 per cent of our cases. The mechanism of the rise is probably best explained on the basis of obstruction to the pancreatic duct. It would seem that as more and more of the pancreatic tissue is replaced by cancerous tissue one may anticipate a concomitant decrease in the serum lipase. In case 259 this mechanism is illustrated. Life was prolonged by cholecystojejunostomy, which relieved the initial jaundice. A progressive decrease in lipase followed. This occurred so quickly during a period of eleven weeks that another explanation suggests itself, namely, that the cholecystojejunostomy caused a subsidence of edema and hence, possibly, a partial release of the pancreatic obstruction. Knowledge of the level of the serum lipase is of no assistance in the differentiation between pancreatitis and carcinoma, although somewhat higher values were present in our cases of acute pancreatitis and in those reported by Comfort⁸. Nor is an elevated serum lipase of great diagnostic assistance in chronic obstructive jaundice. However, in this study carcinoma gave rise to an increase in lipase twice as often as did obstructive jaundice due to gallstones.

Jaundice—Data for serum lipase in various types of jaundice are given in table 2. Loeper and Soulié⁹ have expressed the belief that an inflammatory swelling of the head of the pancreas may accompany catarrhal jaundice. Crandall¹⁰ stated that while an increase in serum

⁸ Comfort, M., and Osterberg, A. E. Lipase and Esterase in the Blood Serum, *J. Lab. & Clin. Med.* **20**: 271 (Dec.) 1934.

⁹ Loeper, M., and Soulié, P. La participation du pancreas au syndrome d'ictère catarrhal, *Nutrition* **6**: 271, 1936.

¹⁰ Crandall, L. A. Origin and Significance of the Blood Serum Enzymes, *Am. J. Digest. Dis. & Nutrition* **2**: 230 (June) 1935.

lipase may accompany experimental hepatic injury no definite hypothesis has been offered to explain the mechanics of the increase. Our experience with patients, many of whom undoubtedly had some degree of hepatocellular injury, affords no support for the observations of Loeper and Soulié and of Crandall. Thirty serum lipase determinations in 15 cases of so-called catarrhal jaundice failed to show an elevated lipase value in a single instance at any time during the course of the disease. Likewise, although hyperthyroidism is frequently associated with evidence of hepatic dysfunction, the values for serum lipase were

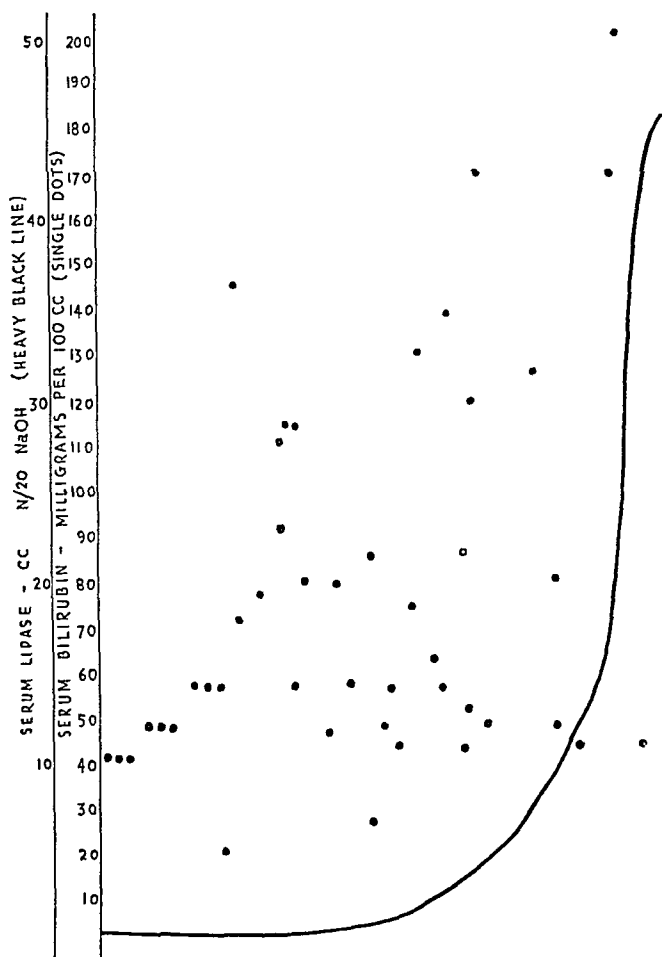
TABLE 2—*Data on Serum Lipase in Cases of Jaundice*

Diagnosis	No of Cases	No of Tests	No of Cases with Values Below 1 Cc	No of Cases with Values Above 1 Cc	Comment
Catarrhal jaundice	15	30	15	0	
Arsenical jaundice	1	6	1	0	
Chronic cholangitis	1	8	1	0	
Hepatitis with pneumonia	1	1	1	0	
Carcinoma of the hepatic ducts	4	5	3	0	
Pericholecystitis	2	2	2	0	
Obstructive jaundice of undetermined origin	3	4	2	1	Case 28 Lipase, 0.8 cc. clinical diagnosis, carcinoma of head of pancreas, no operation or necropsy. Case 55 Lipase 1.2 cc. clinical diagnosis, carcinoma of head of pancreas with diabetes and with metastasis to brain no operation or necropsy. Case 391 Lipase, 0.30 and 0.10 cc., clinical diagnosis carcinoma of head of pancreas no operation or necropsy.
Cancer of ampulla of Vater	1	1	1	0	Case 393 Lipase, 0.48 cc., cancer of ampulla of Vater, questionable involvement of head of pancreas cholecystenterostomy, death no necropsy.
Hyperbilirubinemia (latent icterus)	6	9	5	1	Case 250 Lipase, 1.12 and 9.36 cc. no cause found for hyperbilirubinemia, gallbladder liver and blood normal.

normal in 12 cases of hyperthyroidism in this series (table 5). In 1 case of arsenical hepatitis and in 1 of hepatitis associated with pneumonia there was likewise no elevation in serum lipase. This clinical study supplies no evidence that hepatocellular injury by itself causes an elevation of serum lipase.

If our observations in catarrhal jaundice can be substantiated in a larger series, the test for lipase will be of distinct value in obscure cases of jaundice. An elevated value for lipase possibly can be looked on as militating against a diagnosis of so-called catarrhal jaundice. We are unaware of any previous reference to the use of the test for serum lipase in cases of catarrhal jaundice.

Hyperbilirubinemia and Serum Lipase—We have not encountered any previous report attempting to determine the relation between hyperbilirubinemia and the content of lipase in the blood. In view of the feeling in some quarters that there is a possible connection between hepatocellular function and the amount of circulating lipase, it was decided to determine the effect of hyperbilirubinemia on the degree of lipasemia. We felt that this relation was deserving of investigation in view of the frequency with which, in certain clinical entities, patients



The values for forty-six determinations of serum lipase were plotted against those for a similar number of determinations of elevated serum bilirubin. In each instance both determinations were run on the same day. There is no constant correlation between the values for serum lipase and for elevated serum bilirubin.

with hyperlipasemia also had jaundice. In the accompanying chart 44 determinations of serum bilirubin for jaundiced patients were plotted against a similar number of determinations of serum lipase. In each instance both determinations were done on the same specimen of blood. It seems obvious that there is no consistent correlation between the two values. Six cases of hyperbilirubinemia without clinical jaundice and

without obvious cause for the increase in bilirubin were also studied (table 2). There was no ascertainable evidence of hepatic dysfunction or of gallbladder disease. In only 1 case of this group was there a slight elevation of lipase above the normal level, and that occurred on only one occasion. Similarly, in 4 cases of carcinoma of the hepatic ducts with complete obstructive jaundice (table 2) there was no increase in serum lipase, a further proof of the lack of influence of jaundice on the content of lipase in the blood.

TABLE 3—Data on Serum Lipase in Cases of Disease of the Gallbladder

Diagnosis	No. of Cases	No. of Tests	No. of Cases with Values Below 1 Cc	No. of Cases with Values Above 1 Cc	Comment
Cholelithiasis (a) no jaundice, no history of jaundice, no hyperbilirubinemia	31	35	30	1	Case 386 Lipase, 1.4 and 0.48 cc., possible subacute transient pancreatitis
(b) With jaundice, history of jaundice or hyperbilirubinemia	29	61	20	9	Case 50 Lipase, 3.30, 0.80 and 0.18 cc., first test prior to drainage of common duct. Case 69 Lipase, 0.70 and 2.1 cc., associated Hodgkin's disease. Case 93 Lipase, 2 and 0.6 cc., recurrent attacks suggesting stone in common duct. Case 171 Lipase, 1.30, 1.24 and 0.88 cc. associated pericholecystitis. Case 165 Lipase, 0.72 and 1.92 cc. Case 170 Lipase, 0.72, 1.06 and 0.71 cc. Case 297 Lipase, 2.04 cc. Case 302 Lipase, 0.74, 1.80, 1.38, 1.31 and 0.84 cc., associated acute pancreatitis. Case 375 Lipase, 2.06 and 2.80 cc., complicated by partial intestinal obstruction.
Cancer of the gallbladder	5	9	5	0	In 2 of these cases there was jaundice, but autopsy revealed no pancreatic involvement.
Acute cholecystitis	2	5	1	1	Case 65 See table 7
Chronic cholecystitis with calculi	7	7	7	0	Diagnosis not proved, no operation or autopsy

Diseases of the Gallbladder (table 3).—Lipase determinations were made in 60 proved cases of cholelithiasis. In 31 of these cases the patients were not jaundiced, gave no history of jaundice and had normal serum bilirubin. An elevated serum lipase was noted in only 1 of the 31 cases (3.5 per cent). This low incidence of hyperlipasemia contrasts strikingly with the occurrence of increased values for lipase in 9 (31 per cent) of the remaining 29 cases of cholelithiasis complicated by jaundice at the time of testing or some time previously. We have already pointed out that jaundice or hepatocellular injury of themselves rarely cause an elevation of the serum lipase. It would appear that one can assume safely that hyperlipasemia in cholelithiasis is suggestive of, if not pathognomonic for, an associated pancreatitis. This confirms a common clinical observation that pancreatic involvement is more frequently

encountered in cholelithiasis when the condition is associated with jaundice and with calculus in the common duct In 5 cases of cancer of the gallbladder (2 of which were associated with jaundice) and in 7 cases of chronic noncalculous cholecystitis there were normal values for lipase Of 2 cases of acute cholecystitis, there was an elevated serum lipase in 1 case, in which there was also heart disease with decompensation

TABLE 4—*Data on Serum Lipase in Cases of Chronic Hepatic Disease*

Diagnosis	No of Cases	No of Tests	No of Cases with Values Below 1 Cc	No of Cases with Values Above 1 Cc	Comment
Portal cirrhosis	11	30	7	4	Case 40 Lipase, 11, 056 and 028 cc, associated diabetes death patient not acutely ill at time tests were done Case 176 Lipase, 13 tests with values ranging from 036 to 074 cc, 1 test, 121 cc syphilitic and cardiac factors, possibly not a true portal cirrhosis Case 191 Lipase, 104 and 056 cc, ascites bromsulfalein retention 60 per cent, positive Takata test hypoalbuminemia, clinical recovery for six years Case 376 Lipase, 022, 132, 16 and 174 cc, typical signs and symptoms
Biliary cirrhosis—obstructive and nonobstructive	9	39	8	1	Case 9 Lipase 105 and 206 cc, obstructive biliary cirrhosis, pancreas grossly normal at autopsy
Cirrhosis with hypercholesterinemia	1	1	1	0	Biliary type of cirrhosis with xanthelasmic deposits in skin
Cirrhosis with heart failure	2	3	1	1	Case 119 Lipase, 14 and 08 cc, patient believed to have borderline hepatocellular damage
Hanot's cirrhosis	1	1	0	1	Case 228 Lipase, 102, 142 and 14 cc, woman aged 23 with typical signs and symptoms, jaundice of one year's duration, splenomegaly no ascites and no obstruction
Hemangioma of the liver	1	4	0	1	Case 167 Lipase, 123, 134 and 101 cc, pathologic diagnosis from section removed surgically a fourth test one year later, 014 cc, pancreas not examined
Cancer of the liver (secondary)	1	2	0	1	Case 129 Lipase, 346 and 218 cc, hepatic cancer secondary to cancer of the sigmoid flexure, pancreas normal at operation, severe jaundice, no follow up study

Chronic Hepatic Disease (table 4) —Comfort³ reported increased values for serum lipase in 13 per cent of his cases of hepatic disease He stated the belief that the increase resulted either from destruction of the hepatic parenchyma or from associated pancreatitis Our study throws no additional light on the possible relation of chronic hepatic disease to the serum lipase Twenty-nine per cent (7 cases) of our 24 cases of cirrhosis of the liver were associated with elevated lipase values In only 1 of this group of cases with hyperlipasemia was the pancreas inspected and said to be normal In 2 cases of hepatic tumor the serum lipase was elevated, in 1 the pancreas was reported to have

been of normal shape and consistency at operation. Until a large series of cases of chronic hepatic disease is reported, with values for lipase and with complete protocols of necropsies, we are unwilling to accept the view that the hepatic diseases encountered clinically can be considered a frequent cause of elevations in the serum lipase.

Metabolic and Chronic Granulomatous Diseases (table 5) —These disorders were grouped together in an effort to ascertain whether metabolic disturbances associated with an abnormal level of sugar, fat or protein in the blood showed any tendency to disturb the level of lipase.

TABLE 5—Data on Serum Lipase in Cases of Metabolic and in Chronic Granulomatous Disease

Diagnosis	No of Cases	No of Tests	No of Cases with Values Below 1 Cc	No of Cases with Values Above 1 Cc	Comment
Diabetes mellitus	18	26	14	4	Case 27 Lipase, 1.95 and 1.35 cc associated chronic gastritis. Case 40 Associated portal cirrhosis (see table 4). Case 55 Lipase, 1.20 cc pancreatic cancer not excluded. Case 195 Lipase, 0.62, 1.01 and 0.89 cc.
Carotinemia	1	1	1	0	
Hyperinsulinism	1	1	1	0	Case 143 Pancreatic adenoma at operation, test done in preoperative shock free period.
Xanthomatosis	1	1	1	0	
Hyperthyroidism	12	16	12	0	
Hypothyroidism	16	16	16	0	
Syphilis	27	40	25	2	Case 185 Lipase, 1.42 and 0.28 cc, associated venereal lymphogranuloma. Case 176 Associated portal cirrhosis (see table 4).
Venereal lymphogranuloma	21	25	1 ^a	2	Case 185 See case 185 under syphilis. Case 22 Lipase, 1.2 cc.
Tuberculous peritonitis	2	4	2	0	
Pulmonary tuberculosis	3	3	3	0	

in the serum, in the absence of demonstrable disease of the pancreas. In only 2 (11 per cent) of the cases of uncomplicated diabetes mellitus was there hyperlipasemia. It is probable that this incidence does not exceed that of pancreatitis in patients with diabetes. The preponderance of normal values for lipase in diabetes is of interest because it is known that alteration in fat metabolism¹¹ often accompanies the fundamental disturbance of carbohydrate metabolism in this disease. Hyperthyroidism has been discussed previously. No instance of increase in the serum lipase was encountered in 16 cases of hypothyroidism in spite of the associated hyperlipidemia in many instances. A review of this material

¹¹ Mosenthal, H. O. Pancreatitis and Diabetes. *Ann Int Med* **11** 1001 (Dec) 1937. Soskin, S., and Mirsky, I. A. Medical Treatment of Hyperthyroidism with a High Fat Diet. *J A M A* **110** 1337 (April 23) 1938.

suggests that in the absence of pancreatic disease an increase in blood lipids is not associated with an elevation of the serum lipase

We had the opportunity to study the serum lipase in a large group of cases of venereal lymphogranuloma in which studies of plasma proteins had been carried out by Jones and Rome¹² The hyperglobulinemia so frequently found in this disease was not accompanied by any elevation of the serum lipase In only 2 of 21 cases was there a slight rise above the normal value for lipase

TABLE 6—Data on Serum Lipase in Cases of Malignant Disease

Diagnosis	No of Cases	No of Tests	No of Cases with Values Below 1 Cc	No of Cases with Values Above 1 Cc	Comment
Carcinoma of stomach	13	13	12	1	Case 183 Lipase, 132 cc autopsy showed the pancreas to be free of carcinomatous infiltration, but adjacent lymph glands were involved
Carcinoma of colon	8	9	7	1	Case 129 See comment, table 4
Carcinoma of esophagus or of larynx	2	2	2	0	
Carcinoma of esophagus (partial duodenal obstruction)	1	1	1	0	
Carcinoma of kidney	1	2	1	0	
Sarcoma of jejunum	1	1	1	0	
Lymphosarcoma of ileum	1	2	1	0	
Leiomyosarcoma of stomach	1	1	1	0	
Lymphoblastoma (retroperitoneal)	1	1	1	0	
Lymphosarcoma with obstructive jaundice	1	2	0	1	Case 21 Lipase, 32 and 0.6 cc, previously proved lymphosarcoma with mediastinal involvement which had responded to roentgen therapy, later developments, obstructive jaundice and roentgen and clinical evidence of mass in region of head of pancreas, with tremendous widening of duodenal loop mass and jaundice disappeared after roentgen therapy, first test while jaundiced, second test after recovery
Hodgkin's disease	3	4	2	1	Case 69 Lipase, 0.7 and 2.1 cc, associated cholelithiasis and biliary fistula

In only 2 of 27 cases was syphilis associated with increased serum lipase, in 1 of these venereal lymphogranuloma was also present and in the other hepatic cirrhosis was a complication In 5 cases of tuberculosis the values were normal It appears from the study of this group that the presence of uncomplicated diabetes mellitus, disease of the thyroid, syphilis, venereal lymphogranuloma or tuberculosis exerts no influence on the level of lipase in the blood

¹² Jones, C. A., and Rome, H. P. Serum Proteins, Takata-Ara Reaction, and Liver Function Tests in Lymphogranuloma Venereum, *Am J Clin Path* 9:421 (July) 1939

Malignant Disease (table 6) —A sufficient number of instances of malignancy (32 cases) has been studied to enable us to conclude that malignant disease exerts no effect on the serum lipase. Apparently the associated cachexia and anemia are not factors that disturb the serum lipase. The 4 increased values (cases 183, 129, 69 and 21) in this group can be attributed, we feel, to disturbances of pancreatic function associated with the malignant disease.

TABLE 7—*Data on Serum Lipase in Cases of Disease of the Stomach, Intestines and Heart*

Diagnosis	No of Cases	No of Tests	No of Cases with Values Below 1 Cc	No of Cases with Values Above 1 Cc	Comment
Gastric ulcer	4	6	4	0	
Duodenal ulcer	10	11	9	1	Case 211 Lipase, 1.4 cc., osseous tuberculosis and history suggestive of duodenal ulcer, test taken during ulcer flare up, pancreatic involvement not ruled out
Gastritis or gastroduodenitis	14	17	13	1	Case 27 Lipase, 1.95 and 1.35 cc., associated diabetes mellitus
Functional colonopathies	30	31	30	0	
Ulcerative colitis	1	2	1	0	
Acute colitis (nonspecific)	2	2	2	0	
Ileocolitis	1	1	1	0	
Diverticulosis coli	2	2	2	0	
Duodenal diverticulum	2	2	2	0	
Intestinal obstruction					
(a) Inguinal hernia	1	2	0	1	Case 43 Lipase, 1.7 and 0.6 cc
(b) Ileitis	1	1	0	1	Case 31 Lipase, 1.8 cc
(c) Gallstones	1	2	0	1	Case 375 Lipase, 2.06 and 2.80 cc
(d) Adhesions	1	1	0	1	Case 412 Lipase, 1.96 cc
Heart disease					
Rheumatic					
(a) Decompensated	3	6	2	1	Case 65 Lipase, 1.2, 1.4, 0.4 and 0.68 cc., heart disease associated with an attack of acute cholecystitis
(b) Compensated	3	3	3	0	
Hypertensive	4	4	4	0	
Other	3	3	3	0	

Diseases of the Stomach and Intestines (table 7) —Elevated values for serum lipase have been reported in some cases of duodenal ulcer by Comfort³ and by Jergeson and Simonds.¹³ In 1 (10 per cent) of our cases of suspected duodenal ulcer the lipase was slightly elevated. In only 1 of 14 cases of gastritis and duodenitis was there a rise in lipase and in that case there was associated diabetes. Four patients with gastric ulcer had normal values.

¹³ Jergeson, F. H., and Simonds, J. P. Blood Lipase in Patients with Peptic Ulcer, *J. Lab. & Clin. Med.* **19** 1054 (July) 1934.

In the cases of nonobstructive lesions and functional disorders of the small and large bowel the serum lipase was uniformly normal. The only positive lipase test in this group of 38 cases was obtained in case 27 in which the condition was associated with diabetes.

Intestinal Obstruction (table 7) —We are unable to explain the rise in serum lipase which was encountered in all of the 4 cases of intestinal obstruction which were studied. If observations on a larger series confirm this finding, the test will have an added diagnostic value. It is possible that distention of the duodenum may interfere with the flow of pancreatic juice or that toxins absorbed from above the obstruction may exert a damaging effect on the pancreas or the liver. A more attractive hypothesis would be that there is continued absorption of the lipolytic ferment above the point of obstruction. It is conceivable that the rapidity with which the rise in lipase occurs and the magnitude of the rise may be proportionate to the nearness of the obstruction to the ampulla of Vater.

Heart Disease (table 7) —The data obtained in 10 cases of various types of heart disease offer further confirmation of the consistent normality of the values for lipase found in conditions not associated with pancreatic dysfunction. The lipase values were normal in all cases except 1, in which there were cardiac decompensation and acute cholecystitis and likely some degree of pancreatic inflammation (case 65).

SUMMARY AND CONCLUSION

This report comprises data on 616 independent determinations of serum lipase for 371 patients, performed over a period of three years. The method is described, and its technical difficulties are discussed. Surprisingly uniform results were obtained. In our experience values for serum lipase are significant when they exceed 1 cc of a twentieth normal solution of sodium hydroxide.

A large number of patients with functional and organic disorders but with no clinical, surgical or pathologic evidence of pancreatic disease were examined in order to determine the incidence of positive tests in nonpancreatic disorders. Uniformly normal lipase values were obtained in uncomplicated diabetes mellitus, hyperthyroidism, syphilis, tuberculosis, hypothyroidism, venereal lymphogranuloma, nonpancreatic malignant disease, uncomplicated peptic ulcer, gastritis, gastroduodenitis, functional colonopathies, nonobstructive organic diseases of the small and large intestines and heart disease. The significance of normal values for lipase in these conditions is emphasized in order to stress the specificity of the test as an indication of pancreatic disease.

This study confirms the reports of others that diseases of the pancreas show the highest incidence of increased values for serum lipase. In 9 of 11 cases of acute pancreatitis and in 5 of 8 cases of proved cancer of the pancreas pathologic values for lipase were obtained. Further proof that disease of the pancreas is the usual cause of elevations in serum lipase is supplied by the data for a group of 60 cases of cholelithiasis. A positive test was obtained in only 1 of 31 cases without jaundice and without a previous history of jaundice, whereas in 31 per cent of the remaining 29 cases of cholelithiasis with jaundice or with a history of jaundice values above 10 cc were obtained.

This study does not supply any support for the view¹⁴ that hepatocellular injury causes an elevation of the serum lipase. Normal values were obtained in 15 cases of so-called catarrhal jaundice, 2 cases of toxic or infectious hepatitis and 12 cases of hyperthyroidism. These findings tend to throw some doubt on the theory that hepatic dysfunction may disturb the level of the serum lipase. If our findings in cases of catarrhal jaundice are confirmed by others, the lipase test may prove to be of distinct value in certain cases of jaundice of obscure causation, for an elevated value for serum lipase would tend to exclude the diagnosis of catarrhal jaundice.

As might have been anticipated, we noted no relation between hyperbilirubinemia and the values for serum lipase. This statement is based on simultaneous determinations of serum lipase and bilirubin on the same blood samples from 44 jaundiced patients. The fact may be considered additional evidence against the theory of a hepatic causation for hyperlipasemia.

In chronic hepatic disease associated with widespread destruction of the hepatic parenchyma there was a rather high incidence of hyperlipasemia. High values were obtained in 7 of 24 cases of cirrhosis of the liver and in 2 cases of hepatic tumor. An examination of the material in table 4 does not supply very convincing evidence that the possibility of pancreatic involvement was satisfactorily eliminated. The pancreas was examined at autopsy in only 1 case (9) and was reported to be normal.

Four patients with intestinal obstruction had elevated values for serum lipase. We have found no reports of a similar observation in the literature. If the observation is confirmed by others, the serum lipase test will have another clinical application of importance.

We feel that this study justifies the conclusion that the serum lipase determination is of considerable clinical importance and that a wider application is warranted than it now enjoys.

14 Zuckcr, T. F., Newburger, P. G., and Berg, B. N. The Amylase of Serum in Relation to Functional States of the Pancreas, *Am. J. Physiol.* **102**: 209 (Oct.) 1932.

BASAL INSULIN REQUIREMENT IN DIABETES MELLITUS

HELEN MARTIN, M D

D R DRURY, M D

AND

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LOS ANGELES

Usual methods which control mild diabetes frequently fail when applied to the patient who suffers from a more severe form of the disease. Determinations of dextrose excretion and blood sugar at intervals accurately timed in relation to food and insulin intake usually give sufficiently satisfactory information on which to construct a daily program of diet and insulin. Certain patients are seen, however, who despite such careful determinations cannot be kept in stable equilibrium. The blood sugar of these patients fluctuates widely throughout the day, or they have glycosuria and hyperglycemia sometime during the late hours of the night or early morning. The slow-acting insulins were devised particularly for the purpose of smoothing out these diurnal variations, and both protamine zinc insulin and crystalline insulin have been of great help. Still, many who have written on the subject agree that the "unstable" diabetic patient may continue "unstable" even with a protamine zinc insulin regimen¹.

The most recent trend in diabetic therapy,² however, has been the use of one daily injection of protamine zinc insulin, with or without the addition of regular insulin before breakfast. The guiding feature of satisfactory treatment with protamine zinc insulin, as stated by Tolstoi and Weber,^{2a} is "the maintenance of weight, freedom from symptoms and absence of ketone bodies in the urine. Glycosuria is desirable, as it affords protection from reactions." That postprandial glycosuria will

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1 Wilder, R M, and Wilbur, D L. Diseases of Metabolism and Nutrition. Review of Certain Recent Contributions, Arch Int Med **59** 329-342 (Feb) 1937

2 (a) Tolstoi, E, and Weber, F C. Protamine Zinc Insulin, a Metabolic Study. Treatment in two Cases of Severe Diabetes by Equally and Unequally Divided Diets, with Comments on Criteria for Treatment, Arch Int Med **64**:91-104 (July) 1939. (b) Pollack, H, and Dolger, H. Advantages of Protamine Zinc Insulin Therapy. Dietary Suggestions and Notes on the Management of Cases, Ann Int Med **12** 2010-2021 (June) 1939

occur with this schedule in the person with severe diabetes is well recognized Ricketts³ stated

It is apparent in such cases (severe diabetics) that constant supply of insulin derived from the subcutaneous depot of protamine insulin, although it is able to take care of the endogenous carbohydrate metabolism, needs to be augmented at meal time with extra insulin if the blood sugar is to be kept within normal limits. On the other hand, it is well known that in cases in which the disease is relatively mild the blood sugar can be controlled at all time with protamine insulin alone.

It is our experience that the postprandial glycosuria of patients with severe diabetes receiving one injection of protamine zinc insulin daily does not in any way protect them from severe hypoglycemic reactions between midnight and 4 or 5 a. m., even if the fasting morning blood sugar (at 7 to 8 a. m.) is within normal range (75 to 125 mg per hundred cubic centimeters). The margin of safety in the patient with severe diabetes who has wide variations in the blood sugar content during the day and night is too small. A little excess food may give rise to a hyperglycemia, suddenly associated with ketosis, as we have noted in several patients entering the diabetic service in coma. Careful inquiry has shown that these patients have had no change in the daily amount of insulin and no infections or febrile illnesses to account for the sudden onset of acidosis. An increase in carbohydrate intake, however, was usually admitted. The failure to take the usual amount of food may quickly cause profound hypoglycemia.

The fundamental problem of the harmfulness or innocuousness of wide diurnal fluctuations of blood sugar associated with marked glycosuria cannot be fully settled at present. It seems reasonable to assume that as finely adjusted a mechanism as the normal control of blood sugar cannot be without significance. However, no experimental work to date has adequately proved or disproved this conception. Until this idea is disproved a normal blood sugar curve should be the goal of diabetic therapy, or, as Ricketts³ stated, "The blood sugar curve of the normal individual may be regarded as the result of a completely adequate pancreatic response."

The two major problems in insulin therapy for the person with severe diabetes may then be said to be (a) control of the fluctuations of blood sugar following ingestion of food and (b) prevention of hyperglycemia and glycosuria in the postabsorptive or fasting state. The latter may be defined as the basal insulin requirement, a concept which has arisen from the study of the insulin requirement of depancreatized dogs in the laboratory.⁴

3 Ricketts, H. T. Carbohydrate Tolerance After Protamine Zinc Insulin. Its Bearing on the Physiology of Insulin Secretion, *J. Clin. Investigation* **17**:795-801 (Nov.) 1938.

4 Greeley, P. O. Basal Insulin Requirement of Depancreatized Dogs, *Am. J. Physiol.* **120**: 345-349 (Oct.) 1937.

Depancreatized dogs require, in addition to quickly available insulin to cover the diet, a small, steady supply of insulin to prevent hyperglycemia during the postabsorptive period. The results of an experiment

TABLE 1—*Basal Insulin Requirement in Depancreatized Dog (Weight, 7.3 Kg)*

Time	Blood Sugar, Milligrams per Hundred Cubic Centimeters	Regular Insulin, Units (Intravenous Injections)
8 30 a m	283	
8 45 a m		2
9 40 a m	148	
10 15 a m	111	
10 45 a m	110	
11 45 a m	144	
12 10 p m	210	
12 30 p m		0.2
12 50 p m	161	
1 15 p m	153	
1 40 p m		0.12
1 45 p m	129	
2 15 p m	134	
2 55 p m		0.12
3 15 p m	161	
3 48 p m	110	
3 51 p m		0.16
4 16 p m	112	
4 46 p m	117	
4 48 p m		0.12
5 16 p m	100	
5 46 p m	102	
5 48 p m		0.12
6 15 p m	83	
6 30 p m	78	
6 56 p m		0.08
7 40 p m	87	
7 57 p m		0.08
8 40 p m	105	
9 00 p m		0.08
9 20 p m	112	
9 40 p m	118	
10 00 p m		0.1
10 30 p m	101	
10 48 p m	101	
11 11 p m	105	

TABLE 2—*Fasting Morning Blood Sugar in Depancreatized Dogs Without Insulin to Cover the Night Requirement*

Dog	Blood Sugar, Mg per 100 Cc
1	440
2	348
3	400
4	400
5	400
6	286
7	336
8	270
9	400
10	364
11	400

in which this basal insulin requirement was controlled in a fasting dog by the injection of a small amount of insulin at a constant rate are recorded in table 1. If such insulin is not supplied, the fasting blood sugar values in dogs vary from 300 to 500 mg per hundred cubic

centimeters, as indicated in table 2. The rising blood sugar of the fasting depancreatized dog without insulin may result from the increased metabolism of body protein that is known to occur during the fasting state in the normal as well as in the depancreatized dog⁵ or from hepatic glycogenolysis. Mirsky⁶ stated that one generally accepted function of insulin is its ability to inhibit glycogenolysis induced by various means. This action has been demonstrated by the work of Major and Mann,⁷ who found that the liver of the depancreatized dog can form glycogen when dextrose is given in large amounts but cannot retain it unless insulin is given simultaneously. The dietary requirements of the depancreatized dog are best met by the use of regular insulin, which, as indicated in chart 1, has a period of activity most suitable for the absorption curve of carbohydrate after a meal.⁸ Protamine zinc insulin, with its

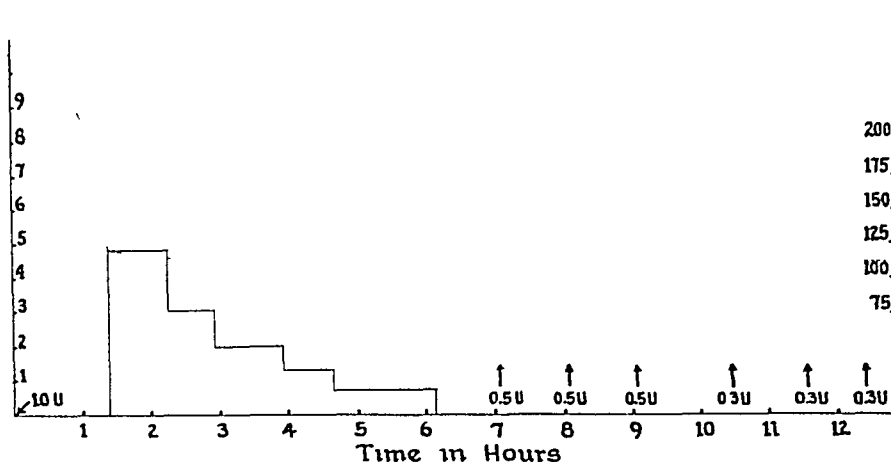


Chart 1—Insulin activity in a depancreatized dog. The dotted line represents blood sugar in milligrams per hundred cubic centimeters of blood. The area enclosed by the solid line represents grams of dextrose given intravenously per hour. The arrows represent times of intravenous injection of regular insulin in amounts as charted.

slower, more prolonged effect,⁹ is more suited to cover the basal insulin requirement.

The observations in depancreatized dogs, it is true, are not always applicable to the diabetic patient, but our experience with animals has

5 Lusk, G. *The Elements of the Science of Nutrition*, ed. 4, Philadelphia, W. B. Saunders Company, 1928.

6 Mirsky, I. A. *The Site and Mechanism of the Antiketogenic Action of Insulin*, *Am J Physiol* **116**: 322-326 (July) 1936.

7 Major, S. G., and Mann, F. C. *The Formation of Glycogen Following Pancreatectomy*, *Am J Physiol* **102**: 409-421 (Nov.) 1932.

8 Drury, D. R., and Greeley, P. O. *The Rate of Disappearance of Insulin from the Body*, abstracted, *Am J Physiol* **126**: 481-482 (July) 1939, *Proc Am Physiol Soc*, 1939, pp. 65-66.

9 Himswoorth, H. P. *Protamine Insulin and Zinc Protamine Insulin in the Treatment of Diabetes Mellitus*, *Brit M J* **1**: 541-546 (March 13) 1937.

led us to believe that by determinations of the basal insulin rate of human beings we might elicit in a comparatively simple way a procedure which would result in more accurate calculations of insulin requirements. If such a procedure could be evolved, many days of trial and error would be saved and a more nearly mathematical calculation would be possible.

The application of the concept of a basal insulin requirement to the diabetic patient has received little attention except by the French workers Baudouin, Lewin and Azérad¹⁰. They stated that normal dogs require 0.05 unit of insulin per kilogram per hour intravenously to produce hypoglycemia. They estimated the normal pancreatic secretion in human beings in the fasting state to be 0.005 unit per kilogram per hour. To reduce the blood sugar to normal in persons with severe diabetes 0.2 to 0.4 unit of insulin per kilogram per hour is necessary. To maintain the blood sugar at a normal level in persons with severe diabetes while fasting 0.01 unit per kilogram per hour is necessary. Lawrence¹¹ also

TABLE 3—*Elevation of Fasting Blood Sugar*

Time	Insulin, in Units	Diet, in Grams			Blood Sugar, Milligrams per Hundred Cubic Centimeters
		Carbo- hydrate	Protein	Fat	
6 p. m.	20	20	25	40	224
8 p. m.					171
10 p. m.					89
12 p. m.					89
4 a. m.					90
8 a. m.					321

appears to have been cognizant of the basal insulin requirement in the person with severe diabetes, as he stated that the sudden elevation of the blood sugar from endogenous sources is no exceptional phenomenon. He frequently observed patients whose blood sugar was about 0.08 per cent late in the evening and over 0.3 per cent the next morning. One case cited by him illustrates this (table 3).

DIVISION OF DIABETIC PATIENTS INTO THOSE WITH AND THOSE WITHOUT A BASAL INSULIN REQUIREMENT

It is axiomatic to state that a patient who receives regular insulin, remains sugar free throughout the day and has a normal blood sugar in

10 Baudouin, A., Lewin, J., and Azerad, E. Injections lentes et continues d'insuline chez les diabetiques, *Presse med* **46** 729-732 (May 7) 1938, Injections continues d'insuline chez les diabetiques. Dose necessaire pour ramener la glycemie à la normale, *Compt rend Soc de biol* **127** 378-380 (Feb 5) 1938, Injections intraveineuses continues d'insuline. Recherche de la dose d'entretien chez trois diabetiques, *ibid* **127** 380-382 (Feb 5) 1938.

11 Lawrence, R. D. Studies of an Insulin-Resistant Diabetic, *Quart J Med* **21** 359-369 (April) 1928.

the early morning before breakfast will have no basal insulin requirement as defined in this paper. In fact, this may be said to be the goal of diabetic therapy, but, as is well known, such a goal is not always attainable if the somewhat hazardous insulin shock is to be avoided. A simple procedure actually will decide which diabetic patients have a basal insulin requirement. This is done by determining the fasting morning blood sugar under the following conditions: no sugar in the urine four to six hours after the evening meal, which has been adequately covered by regular insulin, and no protamine zinc insulin for twenty-four hours. Diabetic patients with high renal thresholds will require in addition a normal blood sugar content six hours after the evening meal. With

TABLE 4—*Determination of Presence or Absence of Basal Insulin Requirement*

CASE	SEX	AGE	Insulin Given, in Units	Urine Sugar, 8 p.m.	Fasting Morning Blood Sugar, Mg per 100 Cc	Basal Insulin Required
1	M	19	20 5 10	Negative	142.8	No
2	F	44	45 35 30	Negative	167.0	Yes
3	F	20	20 0 15	?	235.0	Yes
4	M	20	10 10 10	Negative	167.0	Yes
5	M	48	25 10 10	Negative	160.0	Yes
6	F	56	None	Negative	91.0	No
7	M	23	15 15 15	Negative	156.2	Yes
8	F	61	10 10 10	Negative	208.0	Yes
9	M	56	40 protamine zinc insulin in a.m. 10 and 15 protamine zinc insulin in a.m.	Negative	109.9	No
10	F	72	15 15 15	Negative	124.2	No
11	F	57	10 0 10	Negative	173.9	Yes
12	F	24	15 10 15	Negative	142.8	No
13	F	38	20 20 20	Negative	133.3	No
14	F	38	15 10 10	Negative	121.2	No
15	M	41	10 0 10	Negative	109.9	No
16	F	66	20 0 20	Negative	119.0	No
17	F	58	None	Negative	105.0	No

such requirements fulfilled, a fasting morning blood sugar of 150 mg or more per hundred cubic centimeters indicates the necessity for insulin to cover the basal requirement. The results obtained in a series of diabetic patients in the diabetic service of the Los Angeles County Hospital are presented in table 4.

METHOD OF DETERMINING THE BASAL INSULIN REQUIREMENT

If it is decided that a patient has a basal insulin requirement the procedure is as follows. Whenever possible the fasting blood sugar is brought to a level between 100 and 150 mg per hundred cubic centimeters on the morning of the test by the use of regular insulin six to seven hours previously (midnight), in amounts varying from 5 to 25 units. The exact amount given at midnight depends on the severity of the condition—the patients with least severe diabetes taking 5 units, those with moderately severe, 10 to 20 units, and those with the most

severe, 20 to 30 units (The Folin-Wu micro blood sugar method with 0.1 cc of oxalated venous blood is used because of its convenience in making frequent determinations, although this method gives slightly lower readings than the usual Folin-Wu method) The blood sugar is determined every half-hour to every hour for six or seven hours for the subject who has fasted for twelve hours and has had no protamine zinc insulin for twenty-four to thirty hours Regular insulin is given subcutaneously every hour in the amount estimated to keep the blood sugar between 100 and 150 mg per hundred cubic centimeters The exact amount of insulin required is often difficult to gauge, but practice makes the problem easier In general, however, it has been found that a patient who has been using 50 to 60 units of insulin or less daily has a basal insulin requirement of 1 unit or less per hour, one who has been using between 60 and 100 units of insulin daily has a basal requirement of 1 to 2 units per hour, and one who has been using over 100 units of insulin daily has a basal requirement of 3 to 4 units per hour With this as a general scheme, it is easy to make individual adjustments, for if the level of the hourly blood sugar is rising the amount of the hourly dose of insulin should be increased, or it should be decreased if the blood sugar level is dropping As regular insulin exerts an effect for six to seven hours, the cumulative effect of hourly injections must be borne in mind

The following records have been selected from a group to illustrate the procedure and the results of basal insulin determinations

REPORT OF CASES

CASE 1 (case 6, table 4) —S B, a white woman aged 58, had a history of long-standing mild diabetes On admission she complained that the diabetes was out of control and that she had precordial pain She had had no special diet or insulin prior to entry Her fasting blood sugar twenty-four hours after admission was 214 mg per hundred cubic centimeters She was given insulin and a diet to control the condition After two weeks the administration of insulin was discontinued, and the condition was controlled with a diet of 100 Gm of carbohydrate, 60 Gm of protein and 80 Gm of fat per day

Basal Insulin Study

Time	Blood Sugar, Milligrams per Hundred Cubic Centimeters	Insulin
8 35 a m	91.0	None
10 25 a m	91.0	
10 50 a m	80.0	
11 55 a m	75.5	

This patient represents the very mildly diabetic person, who requires no basal insulin and no dietary insulin

CASE 2 (case 1, table 4) —R B, a white youth aged 19, had had diabetes for one year He had had 25 units of protamine zinc insulin daily, but little attention had

been paid to his diet. He was admitted to the hospital with a severe insulin reaction. The condition was controlled by a diet consisting of 300 Gm of carbohydrate, 80 Gm of fat and 90 Gm of protein per day, with insulin before each meal in doses of 10, 13 and 10 units.

Basal Insulin Study

Time	Blood* Sugar, Milligrams per Hundred Cubic Centimeters	Insulin
8 00 a m	105 0	None
9 50 a m	95 0	
11 45 a m	137 9	
1 45 p m	111 1	
3 30 p m	95 0	

* Capillary blood was used for determinations

This patient required insulin to cover the diet but had no basal insulin requirement.

CASE 3—J Z, a white man aged 27, was admitted to the hospital in diabetic coma. He had had 80 units of protamine zinc insulin per day during the six months prior to entry, but his diet had not been carefully measured. Several days after the acidosis was controlled, the basal insulin requirement was determined.

Basal Insulin Study

Time	Blood Sugar, Milligrams per Hundred Cubic Centimeters	Regular Insulin, Units (Subcutaneously)
7 00 a m	123 5	4
7 30 a m	135 0	
8 00 a m	144 0	
8 30 a m	128 0	2
9 00 a m	119 0	
9 30 a m	133 3	1 5
10 00 a m	118 0	
10 30 a m	118 0	1 5
11 00 a m	102 5	
11 30 a m	87 0	1 5
12 00 a m	81 7	
12 30 p m	81 7	

Fifteen units of regular insulin was given at midnight before the morning of the test in order to have the fasting blood sugar under 150 mg per hundred cubic centimeters. Protamine zinc insulin was not given prior to the study because of its prolonged effect.

As seen by the basal insulin study, this patient had a basal insulin requirement of 1 to 1 5 units per hour. To cover the night requirement of eight to ten hours 15 units of protamine zinc insulin (8 to 10 hours \times 1 5 units per hour) was given at bedtime. The insulin requirement during the day was met by the insulin given to cover the diet. After the study the condition was well controlled with 10 units of regular insulin before each meal plus 15 units of protamine zinc insulin at bedtime, in addition to a daily diet of 150 Gm of carbohydrate, 60 Gm of protein and 75 Gm of fat.

This patient represents a person with moderately severe diabetes, with a basal insulin requirement of 1 to 1 5 units per hour.

CASE 4—U T, a white woman aged 18, entered the hospital with a fracture of the left wrist and the complaint that her diabetes was out of control. She was known

to have had diabetes since she was 14. Prior to entry she had been taking 50 units of protamine zinc insulin and 30 units of regular insulin before breakfast, with a diet of 100 Gm of carbohydrate, 60 Gm of protein and 80 Gm of fat per day. There was 2 to 3 per cent sugar in twenty-four hour urine while she was on this regimen. Her blood sugar on entry was 308 mg per hundred cubic centimeters. The basal insulin requirement was determined.

Basal Insulin Study

Time	Blood Sugar, Milligrams per Hundred Cubic Centimeters	Regular Insulin, Units (Subcutaneously)
7 35 a m	118 0*	
7 40 a m		5
9 05 a m	105 0	
10 12 a m	86 0	
10 45 a m	110 0	
11 53 a m	110 0	
11 55 a m		.1
12 49 p m	120 5	
12 52 p m		1
1 47 p m	105 0	

* Capillary blood was used for this determination. Venous blood was used for the other determinations.

Fifteen units of regular insulin was given at bedtime the night before the study to bring the fasting morning blood sugar to a normal level. (The 5 units given at first was too much, as no further insulin was required for four hours.)

The patient had a basal requirement of 1 unit per hour. The night requirement thus was about 10 units of protamine zinc insulin at bedtime (8 to 10 hours \times 1 unit per hour). The insulin requirement during the day was covered by the dietary insulin.

After study the patient was placed on a diet of 100 Gm of carbohydrate, 75 Gm of protein and 60 Gm of fat per day with 20 units of regular insulin before breakfast, 15 units before lunch and 15 units before dinner and with 15 units of protamine zinc insulin at bedtime. The condition was controlled excellently.

The night basal requirement was determined to be 8 to 10 units, but this was increased to 15 units because of moderate glycosuria after breakfast.

This patient is another illustration of a person with moderately severe diabetes, with a basal insulin requirement of 1 unit per hour.

CASE 5 (case 7, table 4)—P. Q., a white man aged 23, was admitted to the hospital with diabetic acidosis and bronchopneumonia. He had been known to have diabetes for one week but had symptoms of one year's duration. The basal insulin requirement was determined after the pneumonia had subsided.

Basal Insulin Study

Time	Blood Sugar, Milligrams per Hundred Cubic Centimeters	Regular Insulin, Units (Subcutaneously)
8 10 a m	173 9	1 5
9 00 a m	210 5	2
10 00 a m	204 1	2
10 55 a m	200 0	2
12 00 m		2
12 40 p m		2
1 16 p m	163 9	
1 18 p m		2
	169 5	

He was given 15 units of regular insulin at midnight before the test to bring the fasting morning blood sugar to a normal level. He should have had 20 to 25 units, as his fasting morning blood sugar was 173.9 mg per hundred cubic centimeters.

The patient was found to have a high basal insulin requirement, almost 2 units per hour. The night requirement is 15 to 20 units of protamine zinc insulin (8 to 10 hours \times 2 units per hour). The insulin requirement during the day is covered by the dietary insulin. After study the patient was given 25 units of protamine zinc insulin at night (the dose was later decreased to 15 units), and with this regimen the fasting morning blood sugar was 109 mg per hundred cubic centimeters.

At the time this study was made the patient had been afebrile from his pneumonia for four to five days, but a productive cough persisted. With the subsidence of infection the basal requirement of insulin will probably decrease. The condition had not been controlled in the ward until insulin was given at night to cover the basal requirement.

This patient is a good example of those who have a high basal insulin requirement, 2 units per hour.

CASE 6 (case 2, table 4)—M. F., a white woman aged 44, stated on admission to the hospital that her diabetes was out of control and complained of dry gangrene on the tip of the left great toe. She had severe diabetes and had been hospitalized several times because of acidosis. The condition had never been adequately controlled until the basal insulin requirement was determined.

Basal Insulin Study

Time	Blood Sugar, Milligrams per Hundred Cubic Centimeters	Regular Insulin, Units (Subcutaneously)
6 30 a. m.	148.0	3
7 30 a. m.	150.0	3
8 30 a. m.	126.7	3
9 30 a. m.	130.7	3
10 30 a. m.	135.0	3
11 30 a. m.	137.9	3

She was given 20 units of regular insulin at midnight before the test to bring the fasting blood sugar to a normal level.

The basal insulin rate was found to be 3 units per hour. The night requirement was thus 25 to 30 units (8 to 10 hours \times 3 units per hour). The insulin requirement during the day was covered by the dietary insulin. After study the patient was stabilized on a diet of 150 Gm. of carbohydrate, 75 Gm. of protein and 100 Gm. of fat per day, with 45 units of regular insulin before breakfast, 35 units before lunch and 30 units before dinner and 20 units of protamine zinc insulin at bedtime. At first 40 units of protamine zinc insulin was given at bedtime for the night requirement, but this dose was gradually decreased to 20 units. The increased amount was given to aid in controlling the glycosuria which occurred after breakfast.

This patient is an example of the diabetic person who has a high basal insulin rate, 3 units per hour, and a high dietary insulin requirement.

THERAPEUTIC USEFULNESS AND ILLUSTRATIVE RECORDS

The determination as to whether or not a patient has a basal insulin requirement is simple and can be done easily. The actual determination

may at first appear to be an expensive, laborious procedure, primarily of academic interest. With practically all patients studied these factors have been more than compensated for by the decrease in time necessary to establish control in difficult problems or the decrease in total insulin dosage for twenty-four hours, when the right type and spacing of insulin are used.

The criticism will doubtless be raised that four injections daily are required for the control of severe diabetes, and that this is merely a step backward to the regimen advocated in the early days of insulin. However, the advantages of multiple injections of insulin over the single dose are well known. Joslin¹² stated "The more frequently insulin is given, the less is required to produce the same result, because of adjustments to temporary requirements." Holm showed this beautifully with depancreatized dogs.¹³ The inconvenience of the four injections daily is, in our opinion, more than counterbalanced by more adequate control of the condition and reduction of the total insulin requirement frequently attained. It should be emphasized that we are not advocating this regimen for all persons with diabetes, since the majority of patients can be controlled by one or two injections of regular insulin or protamine zinc insulin daily. Rather than a reversion to an old regimen, we feel that the concept of a basal insulin requirement is a new step forward. The old four injection regimen was more or less a "hit or miss" method which was found to be useful but had little rational basis. Consideration of the problem from the standpoint of basal insulin requirement provides a scientific foundation for insulin therapy. Determination of the dosage and time of administration of insulin then become logical. This is essentially the substitution of a rational method for an empiric method.

Patients who have a basal insulin requirement of 1 unit or more per hour require insulin to cover the entire twenty-four hours of the day, in addition to that necessary for covering the dietary intake. The importance of an insulin activity twenty-four hours of the day in the person with severe diabetes has been stressed by Wilder¹³ in a study of the urinary nitrogen excretion in patients with diabetes. He emphasized the point that in severe diabetes azoturia and creatinuria are restrained only during the period of activity of the injected insulin. As regular insulin exerts an effect during a period of from six to seven

12 Joslin, E. P. *The Treatment of Diabetes Mellitus*, ed. 6, Philadelphia, Lea & Febiger, 1937.

13 Wilder, R. M. *Clinical Investigation of Insulins with Prolonged Activity*, *Ann Int Med* **11** 13-29 (July) 1937.

hours (this has been demonstrated by many laboratories), the amount given before meals can be adjusted to cover the insulin requirement in the waking hours. The activity of regular insulin in a diabetic subject is indicated in chart 2. As the peak of activity of regular insulin is within the first two to three hours after injection, this type of insulin is unsuited to requirements during the night, when an insulin exerting a plateau type of activity is most desirable. This activity is best obtained by protamine zinc insulin. For dietary control regular insulin is the correct agent, since its activity curve conforms more closely to the absorption curve of carbohydrate after a meal (chart 2). The activity of regular insulin in a diabetic patient is similar to its action in a depancreatized dog (chart 1). Protamine zinc insulin in our experience¹⁴ has been found unsuited for this dietary requirement in persons with severe

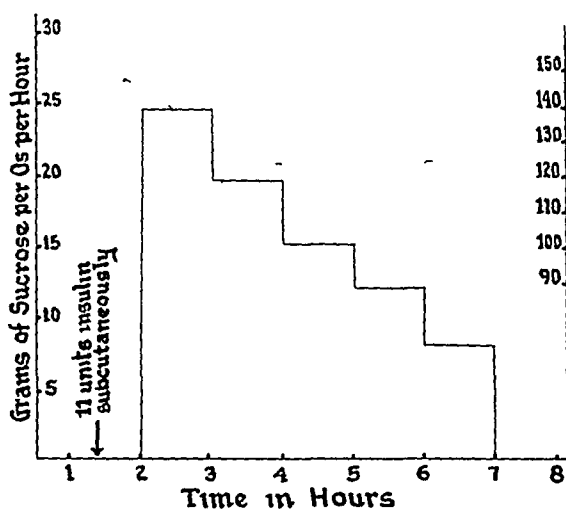


Chart 2—Insulin activity. The dotted line represents blood sugar in milligrams per hundred cubic centimeters. The area enclosed by the solid line represents grams of sucrose given per os per hour. The arrow represents the time of subcutaneous injection of regular insulin.

diabetes, owing to the difficulty in spacing the food intake to cover the period of maximum activity of the protamine zinc insulin without periods of hypoglycemia. This point, as indicated before, will be considered debatable by many, since Joslin¹² stated that protamine zinc insulin is effective in 95 per cent of persons with diabetes. Still, there are indications in his textbook and elsewhere¹⁵ that difficulties in controlling severe diabetes with protamine zinc insulin alone have been encountered. Wilder¹³ noted that the blood sugar is more unstable in patients who

14 Martin, H., and Greeley, P. O. The Problem of Protamine Zinc Insulin Therapy, to be published.

15 Mosenthal, H. O., and Mark, M. F. The Prolonged Use of Protamine Zinc Insulin, *J. A. M. A.* **113** 17-22 (July 1) 1939.

are given protamine zinc insulin when much carbohydrate is included in the diet. The action of each of these types of insulin and the difference in their activities is illustrated by a comparison of chart 3, in which may be seen a curve indicating the activity of protamine zinc insulin in a diabetic patient, with chart 2, which shows the activity of regular insulin in a diabetic patient. In persons with severe diabetes the two roles played by insulin, control of the dietary intake and control of the basal requirement, are provided most satisfactorily by the use of regular insulin to cover the diet and protamine zinc insulin to cover the basal insulin requirement. With knowledge of the basal requirement and of the activity of a given amount of insulin in controlling carbohydrate, patients whose diabetes was previously inadequately controlled have been stabilized easily. (The determination of the amount of insulin necessary to cover the diet will not be discussed in this paper, as it is the subject of

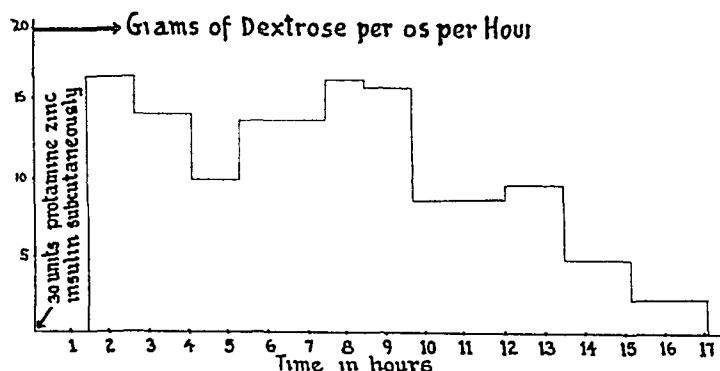


Chart 3—Protamine zinc insulin activity. The area enclosed by the solid line represents grams of dextrose given per os per hour, corrected for errors in failure to maintain the blood sugar level at 100 mg per hundred cubic centimeters of blood. The arrow represents the time of subcutaneous injection of protamine zinc insulin.

another article,¹⁶ but the method by which the activity of a given amount of insulin is determined by repeated blood sugar determinations after ingestion of dextrose is merely a refinement of the method ordinarily followed in adjusting the dietary insulin to cover postprandial glycosuria. The control of severe diabetes in 2 patients by such methods is illustrated by detailed protocols.

CASE 6—Before detailed study the patient (a white woman aged 44) excreted 3.33 per cent, or 52.8 Gm, of sugar in the urine during twenty-four hours when the diet contained 150 Gm of carbohydrate, 60 Gm of protein and 80 Gm of fat, and she received 40 units of regular insulin before breakfast, 25 units before lunch, 25

¹⁶ Drury, D. R., and Martin, H. The Activity of Insulin with Carbohydrate, to be published.

TABLE 5—*Diabetic Control in Case 6*

Time	Blood Sugar, Mg per 100 Cc	Diet, Gm			Insulin, Units	Urine, Cc	Total Sugar in Urine, Gm
		Carbo- hydrate	Protein	Fat			
11 00 a m	133				35 (regular)		
11 35 a m		35	30	40			
1 55 p m	110	15					
3 55 p m	103					650	1 85
4 00 p m					30 (regular)		
4 30 p m		35	20	40			
8 00 p m						500	0 635
8 55 p m	122 6	15					
11 50 p m		8	10	12	20 (protamine zinc)		
2 00 a m	128						
6 00 a m	160					300	0 61
7 00 a m					45 (regular)		
7 30 a m		35	15	20			
9 00 a m	181 8						
10 00 a m		15				300	1 7
10 50 a m	129						
Total		158	85	112	130		4 85

TABLE 6—*Diabetic Control of Patient 3*

Time	Blood Sugar, Mg per 100 Cc	Diet, Gm			Insulin, Units	Urine, Cc	Total Sugar in Urine, Gm
		Carbo- hydrate	Protein	Fat			
12 00 p m					10 (protamine zinc)		
					10 (regular, by error)		
6 00 a m						1,300	0
6 45 a m	80				10 (regular)		
7 00 a m		50	12	15			
9 15 a m	164						
10 40 a m	180				10 (regular)	600	3 4
11 10 a m		50	24	30			
1 15 p m	143					200	1 9
3 00 p m	125					625	2 85
4 00 p m					10 (regular)		
4 30 p m		50	24	30			
8 00 p m						1,600 cc	0
12 00 p m					15 (protamine zinc)		
6 00 a m						1,000	0
Total		150	60	75	65		8 15

units before dinner and 20 units at midnight This represented a dextrose-insulin ratio of 1 11

Carbohydrate in diet	{	Carbohydrate, 150 Gm	}	= 184 Gm
		Carbohydrate from protein, 34 Gm		
Carbohydrate lost in urine				52 Gm
Carbohydrate used				132 Gm
Total insulin used				110 units

The basal insulin requirement was found to be 3 units per hour She was placed on a diet of 150 Gm carbohydrate, 75 Gm protein and 100 Gm of fat daily, with 45 units of insulin before breakfast, 35 units before lunch and 30 units before dinner and 20 units of protamine zinc insulin at bedtime With this dietary and insulin regimen the urinary sugar was practically nil This represents a dextrose-insulin ratio of 1 5

Carbohydrate in diet	{	Carbohydrate from protein, 44 Gm	}	= 194 Gm
		Carbohydrate, 150 Gm		
Carbohydrate lost in urine				5 Gm
Carbohydrate used				193 Gm
Total insulin used				130 units

The excellent control with such a regimen is indicated by the figures in table 5

CASE 3—The patient entered the hospital in diabetic coma He had been receiving 80 units of protamine zinc insulin daily before entry His diet had not been carefully followed The basal insulin requirement of this patient (a white man aged 27) was found to be 1 to 15 units per hour The excellent control obtained by the addition of insulin at night to the dietary insulin is recorded in table 6 His diet consisted of 150 Gm carbohydrate, 60 Gm protein and 75 Gm of fat daily, with 10 units of regular insulin before each meal and 15 units of protamine zinc insulin at midnight

SUMMARY

The basal insulin requirement is defined as the amount of insulin necessary to prevent hyperglycemia and glycosuria in the postabsorptive or fasting state

A simple method has been given by which persons with diabetes may be classified as to their basal insulin requirement

The detailed method by which the basal insulin requirement is determined has been explained, and some records of studies made on patients have been presented as illustrations

The therapeutic usefulness of the application of this principle to the control of severe diabetes not well controlled on other regimens has been emphasized

Protamine zinc insulin given at night has been suggested as the insulin most suited to cover the basal insulin requirement, while regular insulin is most suited to cover the dietary intake in persons with severe diabetes

THE ELECTROCARDIOGRAM IN INSULIN SHOCK

DOUGLAS GOLDMAN, M D

CINCINNATI

The use of extreme states of insulin shock in the treatment of psychiatric patients, particularly of those with schizophrenia, has in the last few years afforded an opportunity to study electrocardiographic changes in presumably normal hearts under the influence of large doses of insulin. Insulin shock therapy was introduced by Sakel¹ in 1933 for patients with hitherto relatively hopeless schizophrenia. After a preliminary period of suspicious aloofness, psychiatrists and physicians interested in mental disease have adopted the method on a large scale because of the brilliant results at times achieved.

The method and technic are given in detail in Sakel's monograph and elsewhere. The usual technic requires patients to be in coma from hypoglycemia for an hour or more. This means that from the time the insulin is injected to the termination of the coma three to five hours elapses, during which severe hypoglycemia is present, with minimum blood sugar values of 10 to 30 mg per hundred cubic centimeters.

Several studies of the electrocardiogram in insulin shock therapy have been reported, but the only one of adequate proportions is that of Hadorn². Some of his observations and conclusions are not in complete agreement with mine. Earlier work by Edwards and Page,³ Bucka, Friedlander and Schaffer,⁴ Soskin, Katz, Strouse and Rubinfeld⁵ and numerous others has preempted any priority that may be claimed for description of individual changes in the electrocardiogram during insulin

From Longview State Hospital, Dr E. A. Baber, Superintendent.

Some of the insulin used in this work was supplied by Eli Lilly & Co. and by E. R. Squibb & Sons.

1. Sakel, M. Pharmacological Shock Treatment of Schizophrenia, translated by J. Wortis, Nervous and Mental Disease Monograph 62, Washington D. C., Nervous and Mental Disease Publishing Company, 1938.

2. Hadorn, W. Untersuchungen des Herzens im hypoglykämischen Schock, Arch. f. Kreislaufforsch. **2** 70, 1937.

3. Edwards, D. J., and Page, I. H. Observations on the Circulation During Hypoglycemia from Large Doses of Insulin, Am. J. Physiol. **69** 177, 1924.

4. Bucka, E., Friedlander, K., and Schaffer, H. Ueber die Einwirkung des Insulins und der Hypoglykämie auf das menschliche Herz. Nach elektrokardiographische Untersuchungen, Ztschr. f. d. ges. exper. Med. **57** 35, 1927, cited by Hadorn².

5. Soskin, S., Katz, L. N., Strouse, S., and Rubinfeld, L. H. Treatment of Elderly Diabetics with Cardiovascular Disease, Arch. Int. Med. **51** 122 (Jan) 1932.

shock Of particular interest in this respect is the work of Bucka, Friedlander and Schaffer Other writers have described numerous instances of untoward clinical effects of insulin on the heart in patients with diabetes, such as anginal attacks⁶ and auricular fibrillation⁵ No complete survey of the literature on the effect of insulin on the electrocardiogram will be attempted in this essay

The chief interest in the recent investigations of the effects on the electrocardiogram in purposefully produced insulin shock is derived from the practically ideal experimental conditions of the treatment, the normal quality of the hearts investigated and the deliberate chronicity with which the treatment is carried out, in spite of what might be considered dangerous and threatening symptoms

METHOD OF INVESTIGATION

Two groups of patients were studied Eleven patients who received insulin shock therapy by the classic Sakel technic were investigated electrocardiographically from time to time throughout their period of treatment and at intervals for several months afterward Tracings were made periodically before the day's injection, again at the fastigium of the treatment in stage 3 or 4 (fig 1) and often again the following morning before the treatment Rest days were taken into consideration, as indicated in individual studies The other group consisted of 7 patients who received huge doses of protamine zinc insulin The dose varied from 50 to 300 units and was given in two equal parts with intervals of twelve hours The patients were often hypoglycemic but almost never comatose and were up and about practically all the time Complete study of this group will be published separately Tracings were made at intervals in the morning before the first dose of insulin and the morning meal and occasionally at other times of the day This group of patients was also followed for several months after cessation of treatment Control tracings before initiation of treatment were taken in both groups A total of some 600 tracings was obtained and studied It is to be noted that no digitalis or other "cardiac" drug was administered at any time to the patients

An amplifier tube apparatus (cardiette) was used throughout the investigation The three classic leads and one chest lead were recorded in every case with rare exceptions necessitated by circumstances The chest lead was recorded with the right arm electrode in the fourth intercostal space just to the left of the sternum and the left leg electrode in place as the "indifferent" electrode Most of the tracings were recorded before the publication of the standardized placement of chest electrodes

⁶ Turner, K B Insulin Shock as the Cause of Cardiac Pain Case Report, *Am Heart J* 5 671, 1930

decided by the American and British Heart Associations, and the routine for the purposes of this study was not changed. The condition of the patients in deep insulin shock made recording of acceptable tracings difficult at times, but patience usually surmounted these difficulties.

Form No. H 11

LONGVIEW STATE HOSPITAL
MEDICAL DEPARTMENT

HYPOGLYCEMIA RECORD

TREATMENT No. 45		DATE 3-7-39																		
NAME C. A. J.	COUNTY	UNITS IN SOLUTION 30	TIME 6:15 DR.																	
Temperature 97.8	6:00	15	30	45	7:00	15	30	45	8:00	15	30	45	9:00	15	30	45	10:00	15	30	45
Pulse rate 80					72				68				80				72			
rhythm																				
volume																				
Perpiration 20					18				18				18				20			
Blood Pressure																				
Stage I																				
Pupils normal																				
Sleepiness					✓	✓	✓	✓	✓											
Hunger																				
Fatigue																				
Sweating						✓														
Stage II																				
Sweating							✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Twitching										✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Sucking movements																				
Exophthalmos										✓	✓	✓	✓							
Grasping																				
Stupor										✓	✓	✓	✓	✓						
Stage III																				
Coma																	✓	✓	✓	✓
Post Babinski																	✓	✓	✓	✓
Pupils																	✓	✓	✓	✓
Athetosis																				
Salivation																	✓	✓	✓	✓
Piloerector Peact																				
Tonic Spasm																				
Stridor																		✓		
Epileptiform Conv.																				
Stage IV																				
Collapse of Nares																				
Fixed Corneal Pupil																				
Loss of Reflexes																				
Patellar																				
Biceps																				
Edin ki																				
Corneal																				
Chvostek's Sign																				
Pupils																				
Pallor																				
Flushing																				
Cyanosis																				
Pleasant																				
Peristalsis																				
Noisy																				

TEMPERATURE

TIME

10:25

METHOD

7/1000 Gauge

BY WHOM

M. W.

Fig 1—Insulin treatment chart

except in extreme instances. Blood sugar was usually determined at approximately the same time the electrocardiogram was recorded.

ELECTROCARDIOGRAPHIC CHANGES PRODUCED BY INSULIN

The electrocardiographic changes will be discussed and illustrated from two points of view. First, modifications of rhythm, wave forms

and voltage produced by insulin will be taken up systematically, second, the progression of these changes as a whole throughout the weeks of treatment will be considered. In this way a true picture of conditions will be more readily demonstrated.

Physical signs were investigated in these patients, but no outstanding or noteworthy evidence of insulin effect on the heart was determined. Changes in rhythm were detectable at times but were much more striking in the electrocardiograms. The blood pressure regularly rose in most cases from 10 to 30 mm of mercury (table 1). No instance of heart failure has occurred in over 12,000 shock treatments in more than 200 patients, nor has there been any evidence of subsequent circulatory embarrassment.⁷ Rarely during the coma apparent circulatory collapse with lowered blood pressure occurs, but this has always responded to treatment with sugar given intravenously.

TABLE 1—*Blood Pressures Before, During and After Insulin Shock*

Patient	Before Insulin 6 00 a m	Two Hours 8 00 a m	Three Hours 9 00 a m	Four Hours 10 00 a m	After Termination of Shock Treatment
S S	108/	115/65	150/90	160/90	140/95
G B	124/88	140/70	160/85	165/95	120/70
R H	134/90	150/80	150/75	160/90	145/85
R T	124/90	145/80	160/80	160/90	140/80
C R	120/80	150/80			105/85
M O	120/80	135/75	150/75		130/80
H M	128/80	154/80	158/80	155/95	140/85
R P	140/90	150/60	162/82	166/76	152/78
R D	126/76	120/60	128/82	160/80	170/110
L M	100/40	134/74	146/88		

Either bradycardia or tachycardia may occur in insulin shock. The effect of insulin on the heart rate depends largely on other effects of the insulin in the person. The patients who show severe and frequent tonic spasms, epileptiform seizures, marked athetosis or other forms of motor hyperactivity have tachycardia, usually of sinus origin but occasionally of other types (fig 2). When the shock produces marked fall in body temperature (sometimes to as low as 90 F) and reduction in general metabolic activity, bradycardia is to be expected. Tachycardia may persist for some time after the cessation of the shock, but bradycardia usually gives way to the normal rate when the shock is terminated.

Auricular flutter and auricular fibrillation (fig 2) are rare occurrences. In my experience they have always been transient and without any recognizable clinical effect. Extrasystoles are occasionally observed during insulin shock. In only 3 instances were they observed by Hadorn in his series, in 2 of which they were ventricular and in 1

⁷ Since this was written 1 patient died suddenly during coma. Autopsy showed numerous minute hemorrhages in the brain and dilatation of the right side of the heart.

auricular In the present series several instances were observed (fig 3) It should be noted that "shock" is not a necessary condition for production of extrasystoles, for the most striking examples are observed in the tracings of 2 patients receiving protamine zinc insulin (fig 3)

The sinuauricular mechanism often undergoes marked changes with consequent disturbance in rhythm Respiratory sinus arrhythmia does not seem of serious significance in the age group usually subjected to this treatment Suppression of the normal activity of the sinus node is a frequent result of insulin hypoglycemia and manifests itself in various ways Bradycardia with abnormal or suppressed P waves suggests activity of rhythm centers more primordial above the node ("sino-

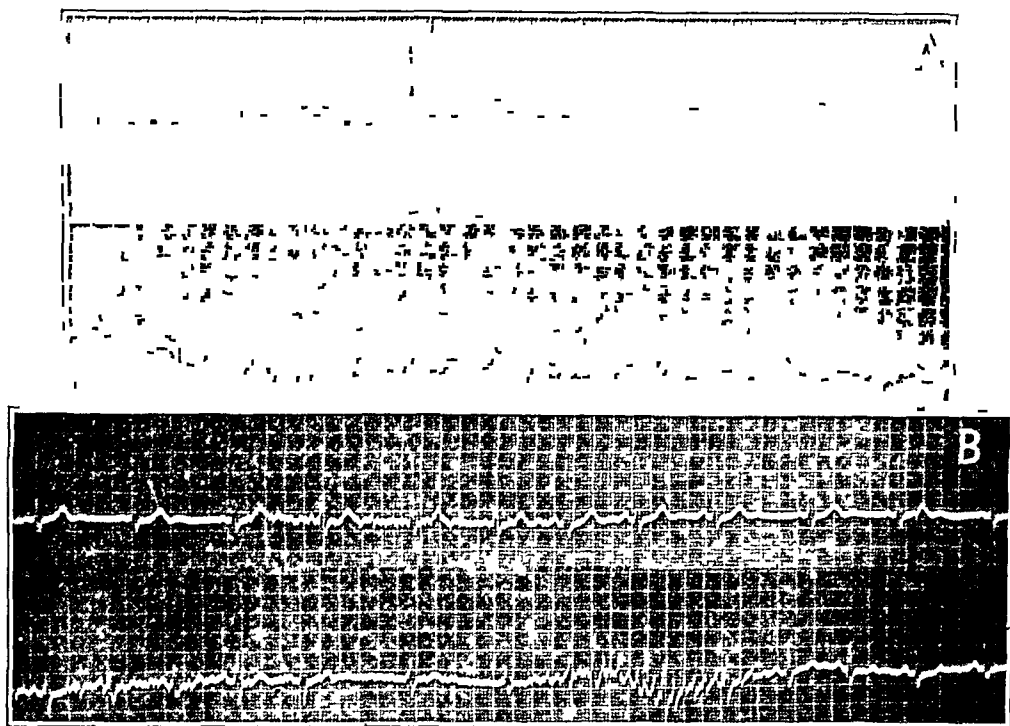


Fig 2—Electrocardiograms of A S A, leads I and II, auricular flutter with occasional dropped beat, thirteenth treatment, stage 3, 50 units of insulin, 17 mg sugar per hundred cubic centimeters of blood, temperature 95 F B, leads II and III, transient auricular fibrillation, forty-first treatment, stage 3, 45 units of insulin, blood sugar 11 mg per hundred cubic centimeters, temperature 96 F

Kaudaler rhythmus") (fig 4) Failure of appearance of the P wave, with a long pause followed by a normal ventricular complex, indicates complete though transient sinuauricular block with ventricular escape (fig 4) Instances of periodic recurrence of ventricular escape with undulating changes in the intervening P waves (fig 4 B) indicate fluctuations in the degree of sinuauricular block which may be quite analogous to the "Wenckebach periods" of low grade auriculoventricular block It is noteworthy that Hadorn stated that he did not observe instances of sinuauricular block in his studies

Increased auricular irritability is manifested in the occurrence of premature auricular contractions (fig 3), auricular flutter (fig 2) and auricular fibrillation (fig 2). These have been transient in the present series, have required no treatment and have resulted in no clinical difficulty.

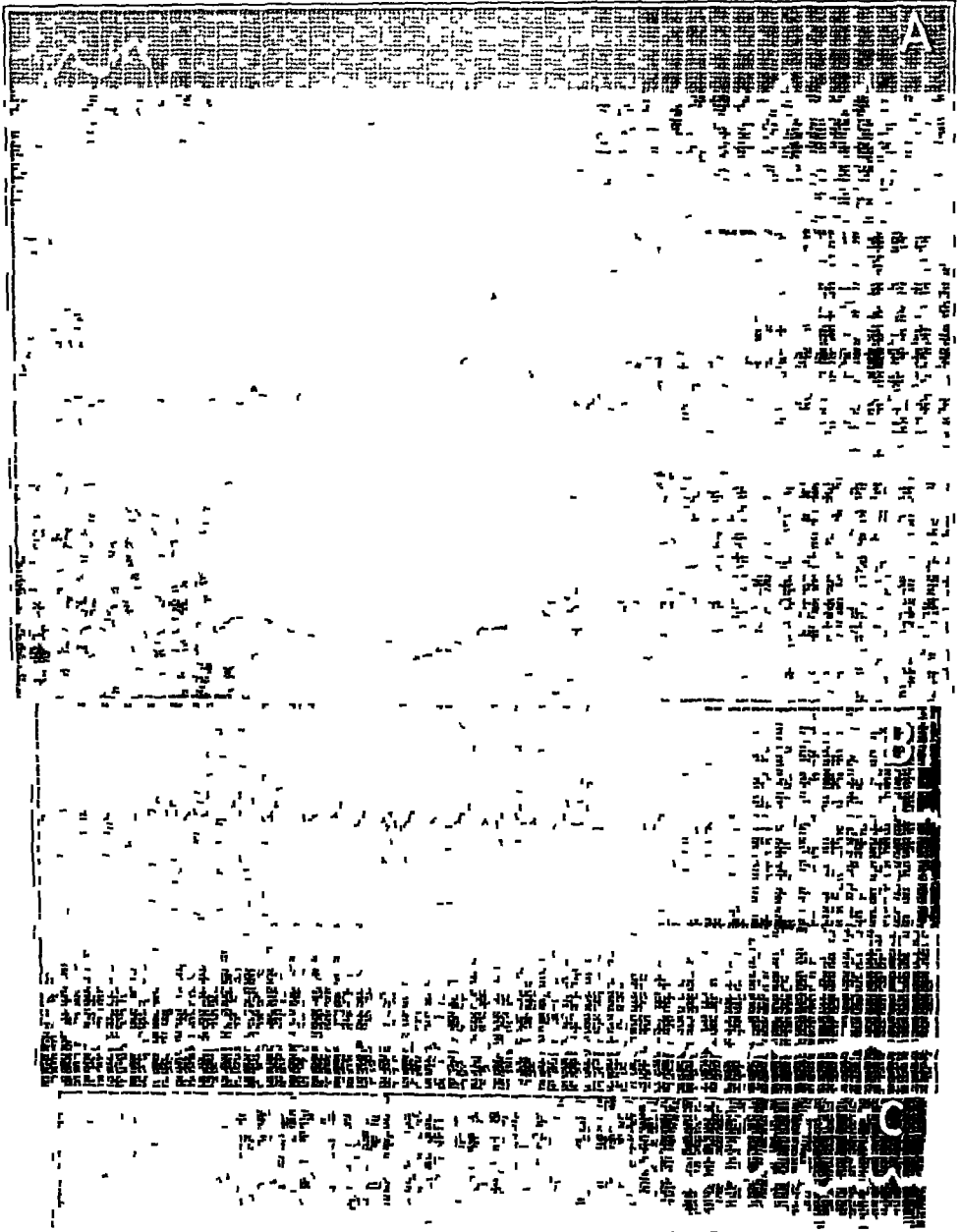


Fig 3—A, J C, arrhythmia, with premature auricular and ventricular contractions and probable sinuaortic block, forty-third treatment, stage 3, 80 units of insulin, blood sugar 6 mg per hundred cubic centimeters, temperature 98.4 F. B, C A, auricular premature contractions, auricular tachycardia, twenty-seventh treatment, stage 3, 60 units of insulin, blood sugar 24 mg per hundred cubic centimeters, temperature 98.2 F. C, L M, ventricular premature contractions with bigeminal rhythm, eighty-sixth day, 150 units of protamine zinc insulin, blood sugar 44 mg per hundred cubic centimeters, temperature 98.8 F.

Disturbance in auriculoventricular conduction was not found in this series except with auricular flutter (fig 2) PR intervals were occasionally apparently shortened (fig 4) Intraventricular conduction in normal auriculoventricular rhythm was never observed to be definitely disturbed, in spite of marked changes in the QRS patterns

The patients receiving protamine zinc insulin showed most of the changes described for patients with regular insulin shock therapy Of importance are the facts that hypoglycemia was usually not nearly so marked in this group and that neurologic symptoms and coma were practically never present at the time tracings were made

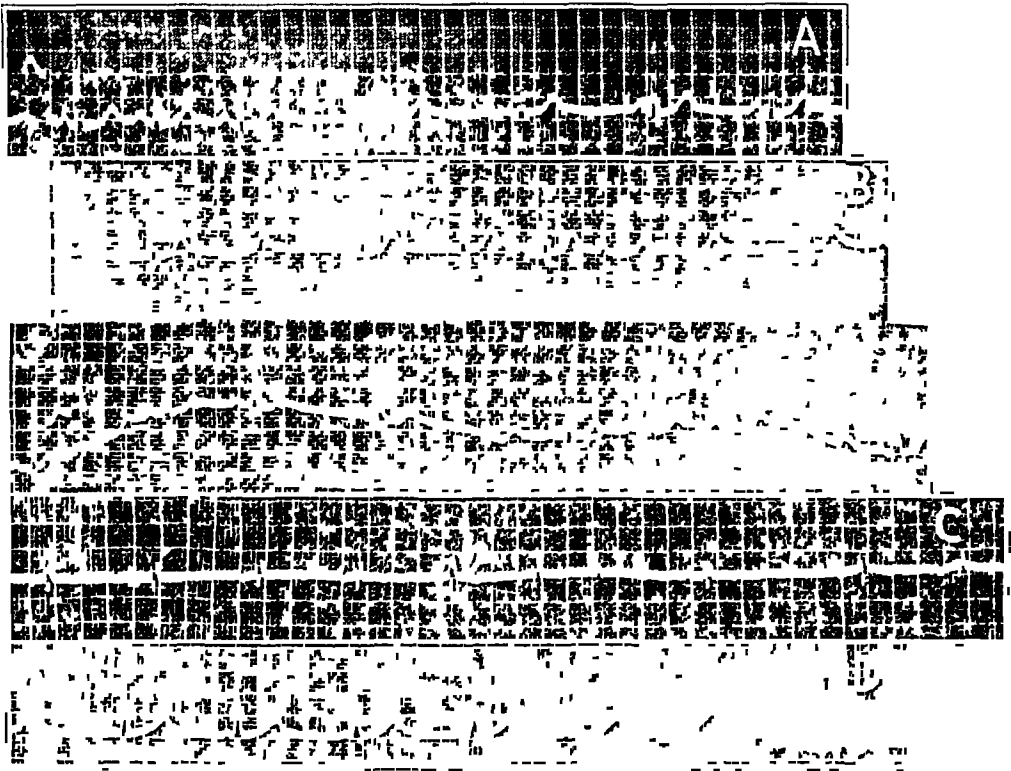


Fig 4—A, J M, apparent ventricular escape from sinuauricular block, twenty-third treatment, stage 3, 65 units of insulin, blood sugar 9 mg per hundred cubic centimeters, temperature 98.4 F B, H W, multiple recurring auricular foci, with occasional ventricular escape, twenty-first treatment, stage 3, 35 units of insulin, blood sugar 10 mg per hundred cubic centimeters, temperature 96.4 F C, C B, before sixty-fifth treatment Note variability of P wave in lead III, indicating probable multiple auricular foci Blood sugar 69 mg per hundred cubic centimeters, temperature 98.6 F D, M E M, fifty-third treatment, stage 3, 120 units of insulin, blood sugar 18 mg per hundred cubic centimeters, temperature 97.4 F Shortened PR interval, 0.08 second

Changes in the P waves were varied and frequent but were not noted in every case Increased P waves in leads II and III, as described by Hadorn, have been observed (fig 5 A and B) Inversion and notching of P waves were not infrequent and when observed they were usually

in leads II, III and IV. The change in the form of the P waves is likely to be progressive and persistent through the course of the treatment. This holds true also for the other changes in wave form about to be described.

Remarkable and striking changes were observed in the QRS complexes in all leads, but the complexes were most widely divergent from

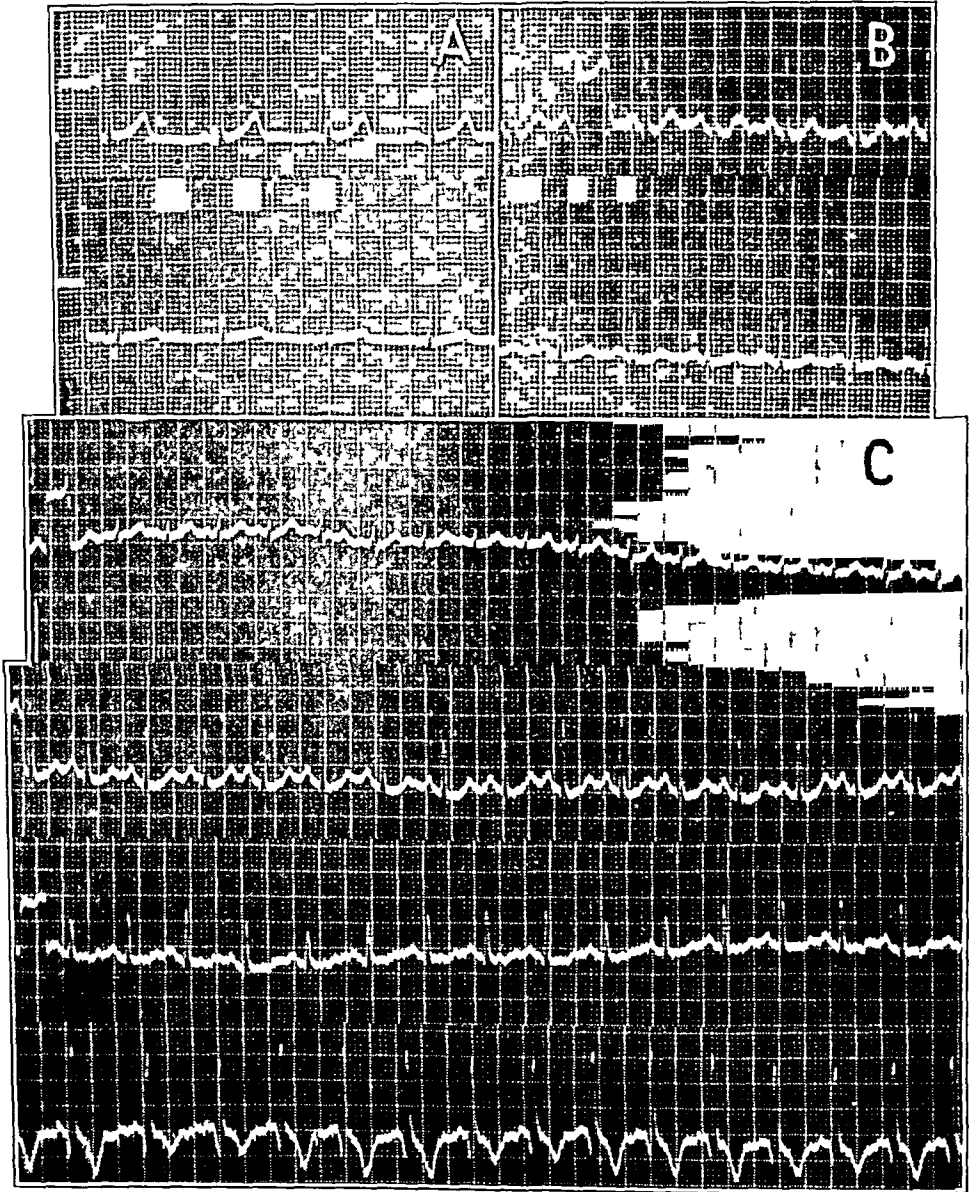


Fig 5—A, C A, before fifty-seventh treatment, blood sugar 75 mg per hundred cubic centimeters, temperature 99.3 F. B, C A, fifty-seventh treatment, stage 3, 75 units of insulin, blood sugar 8 mg per hundred cubic centimeters, temperature 98 F. Tracing B taken at fastigium of shock, with marked tonic spasms. Note increase in P wave in leads II and III from original level. C, B D, forty-first treatment, stage 3, 170 units of insulin, blood sugar 19 mg per hundred cubic centimeters, temperature 94.4 F. Note marked alternation in all leads.

the normal in lead III and in the chest lead. Occasionally moderate increase in voltage in leads I and II was seen during the depth of insulin shock. The most regularly observed change was diminution in voltage or even reversal to negativity of the main deflection. This was most marked at the time of deepest shock, but the effect was cumulative through the series of treatments and in many instances was evident a

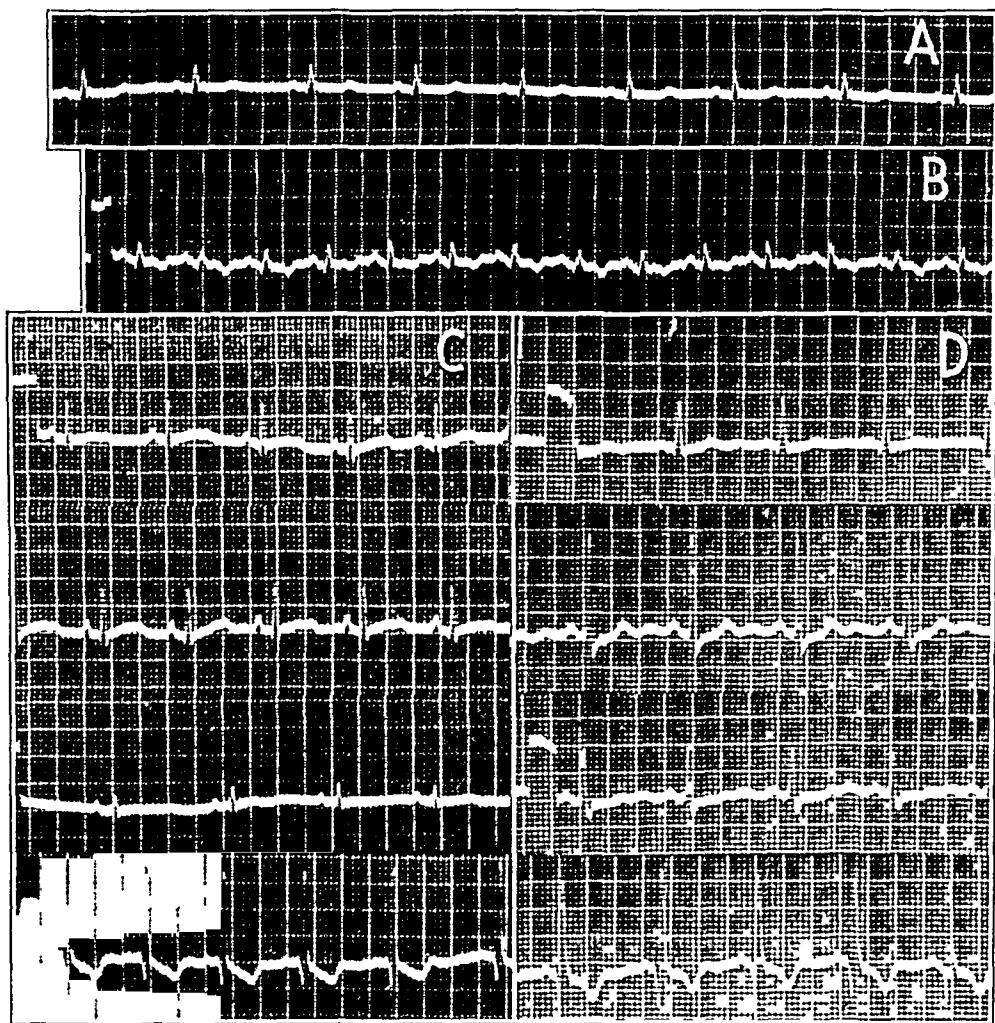


Fig 6—*A, B, D*, control tracing before treatment. *B, B, D*, ninth treatment, stage 3, 200 units of insulin, blood sugar 109 mg per hundred cubic centimeters, temperature 95.6 F. Note fragmentation of QRS in lead III. *C, M, R*, before sixty-third treatment, blood sugar 81 mg per hundred cubic centimeters, temperature 98 F. Note elevated ST segment in leads I and II. *D, A, S*, twenty-first treatment, stage 3, 50 units of insulin, blood sugar 125 mg per hundred cubic centimeters, temperature 95.2 F. Note U wave and marked alternation in leads II and III.

month or more after the final treatment. More significant, perhaps than the change in voltage was the occurrence of marked "phasic" fluctuation in voltage. This was noted in all leads at one time or another.



Fig 7—Electrocardiograms of J M *A*, control tracing before treatment *B*, fortieth treatment, stage 3, 75 units of insulin, blood sugar 11 mg per hundred cubic centimeters Note marked change in T waves in leads III and IV and abnormality of rhythm, probably of supra-auricular origin *C*, six weeks after discontinuing insulin treatment Note change in T wave still evident in leads III and IV



Fig 8—Electrocardiograms of J C *A*, before first injection of insulin, with blood sugar 83 mg per hundred cubic centimeters Note slight abnormality of ST segments in leads II and III *B*, after first injection of insulin (20 units), no coma, blood sugar 29 mg per hundred cubic centimeters T waves in leads I, II and III are definitely depressed *C*, twenty-ninth treatment, stage 3, 90 units of insulin, blood sugar 12 mg per hundred cubic centimeters Note auricular arrhythmia with and without marked tachycardia *D*, before forty-third treatment, blood sugar 81 mg per hundred cubic centimeters Note elevation in ST segment and marked irregular alternation in chest lead The T wave in lead III is practically isoelectric *E*, control tracing ten days after discontinuing treatment Note persistence of the inverted T wave in lead III *F*, control tracing taken six months after discontinuing treatment The T wave in lead III remains inverted

but again was most striking in lead III, where the main deflection may vary from positive to negative within a few beats (fig 5 C). It seems impossible that this fluctuation should indicate grave physiologic disturbance in the myocardium, since it reflects no clinical symptoms. Shift of the electric axis with respiratory phase is the probable explanation for this phenomenon.

Besides change in voltage, the QRS deflections underwent marked metamorphosis during the weeks of treatment. Fragmentation of originally normal complexes with production of "w" complexes and other bizarre forms was frequent. Prominent Q and S deflections occurred, but with no regularity (fig 6 A and B).

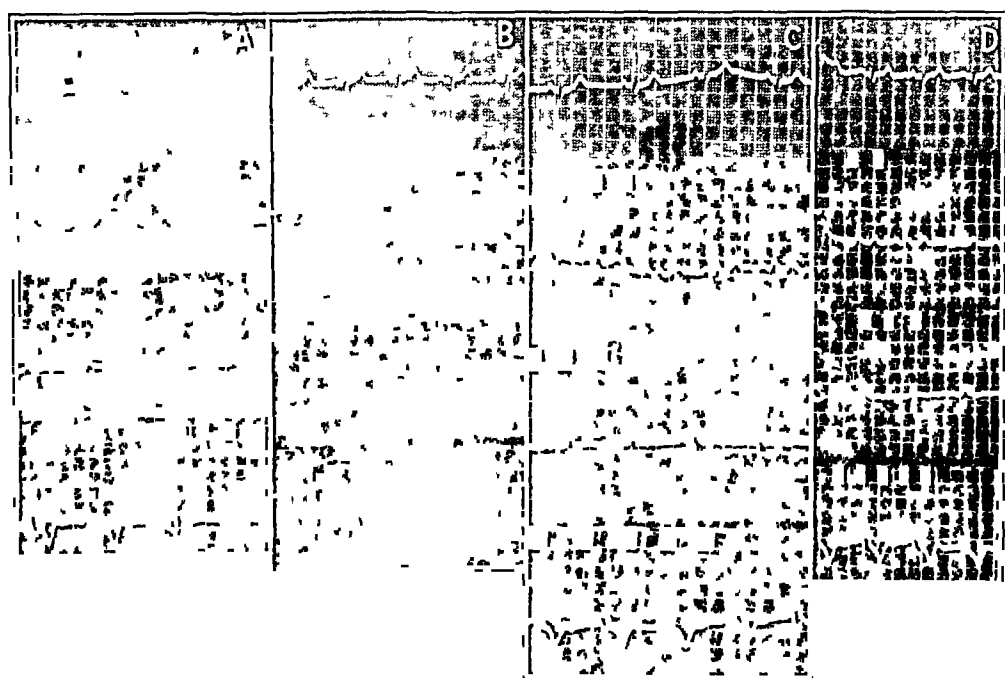


Fig 9—Electrocardiograms of C B A, control tracing before first injection of insulin. Note the "W" form of the QRS segment in lead III. B, before ninety-first treatment, blood sugar 65 mg per hundred cubic centimeters. Note inversion of the T wave in lead III. Note the U wave in the chest lead. C, ninety-first treatment, stage 3, 150 units of insulin, blood sugar 12 mg per hundred cubic centimeters. Note marked alternation in lead III, with respiratory rhythm. The T wave in lead III is isoelectric or diphasic. D, control tracing six weeks after discontinuing treatment. Note that the T wave in lead III is still inverted and that the QRS segment in lead III has not yet returned to its original form.

ST intervals and T waves showed marked changes from the normal during hypoglycemia, with progressive cumulative deviation through the course of the treatment. Elevation or depression of the ST interval was most frequent in leads II and III (fig 6 C). Depression and inversion of the T wave was the most characteristic change observed in practically every patient under the influence of insulin, and it persisted after it was

well established by repeated shock periods, even after rest days. The return to normal often takes several months, according to the present observations, in spite of the opinion of previous authors that the inverted T wave of insulin shock is quickly reversible after termination of hypoglycemia (figs 7, 8, 9 and 10).

A common observation in hypoglycemia was the "u" wave (fig 6 D), which was of varying depth and was found in any lead, particularly in lead III and the chest lead. The addition of this undulation to the electrocardiogram is unexplained, but it is noteworthy that it was one of the striking and persistent effects of hypoglycemia in many cases.

Prolongation of the duration of systole (after correction for the heart rate) was noted at times. This was determined by calculation according to one of several available formulas after measurement of the "QT"

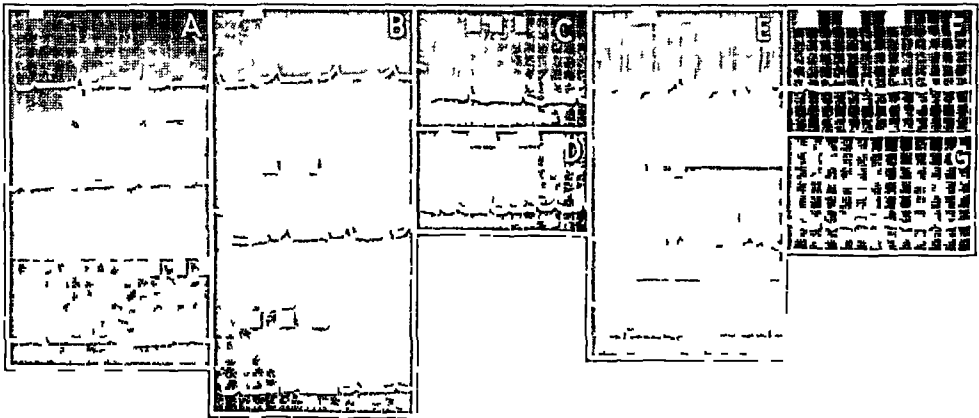


Fig 10—Electrocardiograms of L. M. A, control tracing before treatment. Note abnormalities of the QRS segment in lead III and the depressed ST segment in leads I and II. B, sixth day of treatment, 75 units of protamine zinc insulin daily. Before insulin and fasting in the morning, blood sugar 82 mg per hundred cubic centimeters. This tracing has a more normal appearance than the control, but note the elevation of the ST segment in leads I, II and III. C, thirty-fourth day of treatment, 125 units of protamine zinc insulin, fasting blood sugar 56 mg per hundred cubic centimeters. The T wave in lead III is inverted. D, forty-fifth day of treatment, 125 units of protamine zinc insulin, blood sugar 131 mg per hundred cubic centimeters after noon meal. The T wave in lead III is upright, and there is definite elevation of the ST segment in lead III. E, eighty-sixth day of treatment, 150 units of insulin, blood sugar 44 mg per hundred cubic centimeters after noon meal. The T wave in lead III is inverted, with normal beats, upright with premature ventricular contractions ("coupled" with normal beats, evident in all leads). Note "fragmentation" of the QRS segment in lead III. F, control tracing after discontinuing treatment three days. The T wave in lead III is still inverted and the QRS segment is fragmented. G, control tracing four months after discontinuing treatment. The QRS segment in lead III is still fragmented, the T wave in lead III is isoelectric.

time The formula of Bazett⁸ is most commonly used in the American and English literature $\text{systole} = K \sqrt{\text{cycle}}$ The relative duration of systole is indicated by the value of K The changes in 2 cases are indicated in table 2 Definite prolongation of the period of systolic contraction is not present in every case during insulin hypoglycemia but is sufficiently frequent to indicate that it is a frequent characteristic of the electrocardiogram during hypoglycemia therapy This was noted also by Hadorn

TABLE 2—*Effect of Insulin on Duration of Systole ($K = \frac{\text{Systole}}{\sqrt{\text{cycle}}}$ The Duration of the Systole and the Total Cycle is Determined in Seconds)*

Patient	Date	Duration of Systole, in Seconds		Insulin, in Units
		Before Insulin	During "Shock"	
J C	June 3	0.38		Control
	7	0.40		15
	8	0.40	0.44	25
	14	0.37	0.59	120 (no coma)
	25	0.42	0.40	150 (no coma)
	July 3	0.41	0.39	70
	16	0.415	0.42	90
	31	0.40	0.43	80
	Aug 15	0.44	0.38	110
	Sept 3	0.40		Control
	Oct 18	0.41		Control
	Feb 24	0.41		Control
M E M	July 5	0.41		Control
	16	0.45	0.58	130
	31	0.44	0.43	85
	Aug 16	0.46	0.47	75
	30	0.45	0.57	140
	Sept 11	0.46	0.61	120
	21	0.52		Control
	Oct 17	0.45		Control

COMMENT

The changes in the electrocardiogram resulting from insulin hypoglycemia are not merely daily recurring deviations from a constant normal pattern but are progressive and cumulative from day to day and only slowly recede to the control level after cessation of treatment Several abstracted series of tracings are illustrated (figs 7, 8, 9 and 10) It is evident that changes in the various waves are produced by small doses of insulin in some instances, but in the early stages of the treatment the changes disappear to a great extent by the next morning As the series of repeated hypoglycemic shocks progresses, however the

⁸ Bazett, H. C. An Analysis of the Time Relation of Electrocardiographs, *Heart* 7:353, 1920

changes become less reversible. Both the tracings before the individual shock period and those at the fastigium of hypoglycemia show marked deviation from the control levels. The tracing taken during the period of deepest hypoglycemia shows changes over and above those at the preliminary level, as might be expected, but after each treatment the pattern does not quite revert to the pretreatment level. Return of the electrocardiographic pattern to the appearance previous to treatment is most often slow. Some changes may be evident as long as six months after cessation of treatment (fig 8). No clinical evidence of change in the myocardium could be determined in any of the patients treated in my series, which now exceeds 200 cases. No congestive or anginal symptoms have been evident, and no changes in the sounds have been observed.

The mechanism of the electrocardiographic changes is only vaguely suggested by the studies here recorded. The questions that arise are 1. What changes represent response to alteration in the mechanical conditions faced by the heart? 2. What changes represent fundamental physicochemical alterations in myocardial contraction?

The possible changes in circulatory mechanics that take place during insulin shock are limited. A moderate rise in systolic and diastolic pressure is common (table 1), but this is hardly to be held accountable for the electrocardiographic changes. Tonic muscle spasms involving all the somatic musculature intermittently may at times offer some hindrance to the venous return from respiratory obstruction with increased intrathoracic pressure. Increased blood flow in the arms has been shown.⁹

Intermediate between purely mechanical and purely chemical changes in heart action is the effect of asphyxia. This condition can play but a small part in the electrocardiographic changes, for actual asphyxia takes place in hypoglycemic shock only during epileptiform seizures, which are not so common that they can be considered a source of frequent electrocardiographic changes.¹⁰ No distinction in tracings was noted between the patients in this series who had and those who did not have epileptiform seizures. Certainly changes in the tracings of patients who were treated with huge doses of protamine zinc insulin and practically never became comatose cannot be ascribed to any mechanical impedence to heart action or to asphyxia.

Whether insulin itself, the consequent hypoglycemia or perhaps some factor brought out in reaction to these is responsible for the electrocardiographic changes has been a controversial point since electrocardio-

⁹ Abramson, D. I., Schkloven, N., Margolis, M. N., and Mirsky, I. A. Influence of Massive Doses of Insulin on Peripheral Blood Flow in Man, *Am J Physiol* **128**: 124, 1939.

¹⁰ Goldman, D. Epileptiform Seizures in Insulin Shock Therapy, *J Nerv & Ment Dis* **90**: 765, 1939.

graphic changes resulting from insulin therapy were first recognized. Reactive epinephrinemia has been hypothesized, and certain work¹¹ indicates that it actually occurs. Without attempting to settle the questions involved with any finality the following evidence is to be considered. Large doses of protamine zinc insulin with only moderate hypoglycemia cause marked electrocardiographic changes, hardly less than the changes evident during deep hypoglycemic shock. Small doses of insulin can produce changes as abnormal as those produced by large doses. Finally, after cessation of all treatment the electrocardiographic changes recede only over a period of weeks or months, in spite of the absence of any hypoglycemia or excessive measurable insulin physiologically available. Depression or inversion of the T wave often, though not always, seems to be a function of lowered blood sugar.⁵ Figure 10 shows, for a patient who was given protamine zinc insulin, an upright T wave in lead III associated with normal blood sugar, while tracings taken before and after this show an inverted T wave in lead III, associated with low blood sugar.

Probably an important factor in the electrocardiographic changes is the deviation of carbohydrate oxidation brought on by excessive insulin or by the absence of available carbohydrate or by both. That marked muscular exertion can be maintained under such conditions (tonic spasms or epileptiform seizures) has important metabolic implications. Indeed, increased oxygen (O_2) content of venous blood has been observed during hypoglycemic shock by various investigators,¹² presumably indicating reduced oxygen consumption.

It is possible that a variety of glycolytic, "anaerobic" activity is substituted for the usual oxidation mechanisms. A fundamental change in the chemical dynamics of myocardial activity such as this could be expected to show itself in altered electrical manifestations. Further investigation in this direction seems definitely indicated. The earlier investigations of the effect of insulin in perfused hearts, such as the experiments of Hepburn and Latchford,¹³ throw little light on the possibilities, although the marked increase in sugar consumption noted by these authors after addition of insulin to the perfusion fluid is undoubtedly in some way significant.

11 Tietz, E. B., Dornheggen, H., and Goldman, D. Blood Adrenalin Levels During Insulin Shock Treatments for Schizophrenia, *Endocrinology* **26** 641, 1940.

12 Gellhorn, E. The Action of Hypoglycemia on the Central Nervous System and the Problem of Schizophrenia from the Physiologic Point of View, *J. A. M. A.* **110** 1433 (April 30) 1938. Himwich, H. E., and Fazekas, J. F. The Effect of Hypoglycemia on the Metabolism of the Brain, *Endocrinology* **21** 800, 1937.

13 Hepburn, J., and Latchford, L. K. Effect of Insulin on the Sugar Consumption of the Isolated Surviving Rabbit Heart, *Am. J. Physiol.* **62** 177, 1922.

The effects observed in this and in other investigations of the effect of insulin on the electrocardiogram are in some respects similar to those noted in cases of vitamin B deficiency,¹⁴ alkalosis¹⁵ and adrenalinemia¹⁶. It is reasonable to believe that a common factor in such electrocardiographic changes is a distortion of the normal chemical dynamics of myocardial contraction.

SUMMARY

The electrocardiographic changes associated with the new insulin shock therapy are described in some detail.

The changes produced are persistent for a time even after cessation of the treatment, but they are not permanent.

No clinical cardiologic changes of significance are produced in the patients.

Changes in the chemical dynamics of myocardial contraction are suggested as the probable cause of the electrocardiographic changes.

14 Dustin, C. C., Weyler, H., and Roberts, C. P. Electrocardiographic Changes in Vitamin B Deficiency, *New England J. Med.* **220** 15, 1939.

15 Barker, P. S., Shrader, E. L., and Ronzoni, E. The Effects of Alkalosis and of Acidosis upon the Human Electrocardiogram, *Am. Heart J.* **17** 169, 1938.

16 Milles, G., and Smith, P. W. Effects of Epinephrine on the Heart, *Am. Heart J.* **14** 198, 1937.

DERMATOMYOSITIS AND SYSTEMIC LUPUS ERYTHEMATOSUS

I A CLINICAL REPORT OF "TRANSITIONAL" CASES, WITH A CON- SIDERATION OF LEAD AS A POSSIBLE ETIOLOGIC FACTOR

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During the past few years there has sprung up an abundant literature devoted to the subject of dermatomyositis. Despite this, it is commonly believed that this condition is extremely rare. Early in the course of my studies on lupus erythematosus¹ it became apparent to me that there were resemblances between that disease and dermatomyositis. The belief that this was so was based on observations made in cases showing certain similarities in eruption, clinical course, general outcome and especially the occurrence of what seemed to be "transitional" conditions. Contrariwise, there were also encountered many features that appeared to provide fundamental points of distinction, particularly if one considered only typical examples of each disease. In following the courses in such cases it was not uncommon to find that the nature of the clinical picture was often variously interpreted by the dermatologist, internist, pediatrician, neurologist and even the orthopedist. This is also demonstrated in the literature, which has become complicated by the recording of examples of these diseases or manifestations of them under a plenitude of titles. In addition, there are many reported cases in which the original diagnosis was later supplanted by another one, owing to changes in the conceptions held by the individual observer or to the appearance of additional, and apparently different, clinical features. A critical review of the older literature on this and related subjects shows clearly that there is need for a reevaluation of much data that have played a notable part in the formulation of some of the present accepted beliefs.

1 Keil, H. (a) Relationship Between Lupus Erythematosus and Tuberculosis. A Critical Review Based on Observations at Necropsy, Arch Dermat & Syph **28** 765 (Dec) 1933, (b) Conception of Lupus Erythematosus and Its Morphologic Variants, with Particular Reference to "Systemic" Lupus Erythematosus, *ibid* **36** 729 (Oct) 1937, (c) Relation Between "Systemic" Lupus Erythematosus and a Peculiar Form of Thrombocytopenic Purpura, Brit J Dermat **49** 221, 1937, (d) The So-Called Libman-Sacks Syndrome, Arch Dermat & Syph **34** 124 (Jan) 1936, (e) Tuberculous Skin Lesions New England J Med **218** 783, 1938

In this paper, however, it will be my principal purpose to record in detail several unusual cases illustrating "transitional" conditions, together with the results of a personal follow-up study of a number of instances already described or mentioned briefly in the literature. These protocols were selected to depict the manifold phases of this group of anomalies, and additional examples will be mentioned only as they bear on the elaboration of certain points.

REPORT OF CASE 1

The patient was observed on many occasions by a number of dermatologists who, though recognizing the peculiarities in the clinical course of his condition, were unable to agree on a definite diagnosis. The disease presented by him was first described on May 18, 1931, at a meeting of the Brooklyn Dermatological Society, as a possible example of porokeratosis (?)². At this time the patient was 19 years old, a pressman, and complained of a rash of one year's duration. There was a reddish and violaceous eruption from the tips of the fingers to the wrists. Over the metacarpal and phalangeal joints there were ovoid, well defined, glistening patches characterized by exaggeration of the cutaneous lines (?) as well as by dry, hard, adherent scales and slightly infiltrated borders. The palmar surfaces of the fingers and the skin over the elbows revealed lesions similar to those just described but irregular in shape and redder. A few pinhead scars were observed on the palms. The clinical appearance seemed not to bear out the usual description of porokeratosis, and the diagnosis was based on a biopsy report, which read as follows: "The section showed a persistence of the elastic tissue. The hematoxylin stain showed an epidermis that was acanthotic, with several horny plugs at the follicle openings. There was a peculiar lamellation of the horny layer which was very much thickened. Blood vessels were dilated and surrounded by moderate cellular exudate. The diagnosis was porokeratosis." Roentgenograms of the hands disclosed no abnormal changes in the bones. Notwithstanding the histologic report, most of the observers present regarded the condition as one of acute disseminated lupus erythematosus. The interesting points recorded in the discussion were that the atrophic areas over the elbows were analogous to those observed in acrodermatitis chronica atrophicans or epidermolysis bullosa (Chargin), that there were lesions in the oral mucous membranes (Abramowitz), and that there was atrophy of the thenar eminences (Lyons). The occurrence of a systemic reaction was noted by one of the men, who remarked that the patient seemed to be ill.

Several months later the patient was examined again. The history obtained at this time was of great interest. At the age of 10 years he had an attack of scarlet fever accompanied by sinusitis (right antrum). From the age of 14 years he passed urine once nightly. Two years before the present observation he began to work in a printer's shop. He enjoyed good health until five months later when, after handling lead material, printer's ink and other chemicals, he noticed an erythematous rash over the hands, wrists and elbows, it was most marked over the tips of the fingers, which were extremely tender, a circumstance attributed to the local use of "cre-solvent". A group of observers were led, on the basis of this history, to regard the condition as one of dermatitis venenata, possibly due to printer's ink. The patient began to lose weight gradually. About eight months

² Berkowitz, B. B. Case of Porokeratosis? Arch Dermat & Syph 24 1124 (Dec) 1931

before the present observation, the rash over the elbows became more conspicuous, and fresh lesions appeared on the face. The eruption on the hands faded slowly until it attained its present state. It was difficult for the patient to make a fist, and he complained of pains about the knuckles, wrists and knees. He also noticed thinning of the musculature of the hands. There were no peripheral palsies or wrist drop. He suffered from palpitation and dyspnea on exertion.

On examination the patient did not appear to be acutely ill. There was a generalized eruption showing the following attributes. On the cheeks and nose there was a faint and diffuse erythematous lesion, slightly scaly, spread in a "butterfly" configuration over the "flush area" and accompanied by a light brownish pigmentation (fig 1). Atrophy was absent. The margins of the ears showed

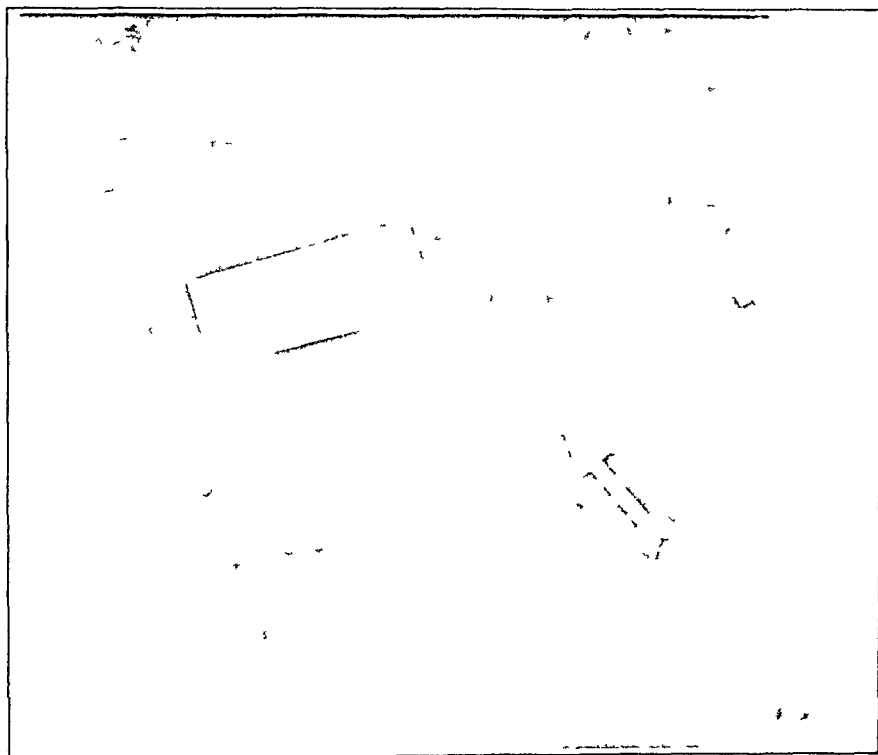


Fig 1 (case 1)—Erythematous lesions in a case of dermatomyositis. One arrow points to a lesion on the ear, the other to an area of light brown pigmentation in "butterfly" configuration.

pea-sized, erythematous, atrophic areas covered with dry, adherent scales (fig 1). The external aspects of the regions of the elbows were sites of large, bluish red, atrophic patches, smooth and somewhat scaly, resembling those associated with *acrodermatitis chronica atrophicans* or the healed stage of *epidermolysis bullosa* (fig 2). The palms and especially the fingers showed superficial, small, erythematous lesions, marked by adherent scales and atrophy in some areas. Noteworthy were the smooth, atrophic, shiny patches over the knuckles (fig 3), these revealed fine telangiectatic vessels over the surface. On the hard palate and the dorsum of the tongue there were a few small, red lesions, superficially denuded and with telangiectasia in occasional areas. The scalp and nails were not affected.

Examination of the heart revealed a snapping first sound at the apex, the second pulmonic sound was louder than the second aortic sound. The temperature was 99 F and the pulse rate 110. Lymph nodes the size of a hazelnut were

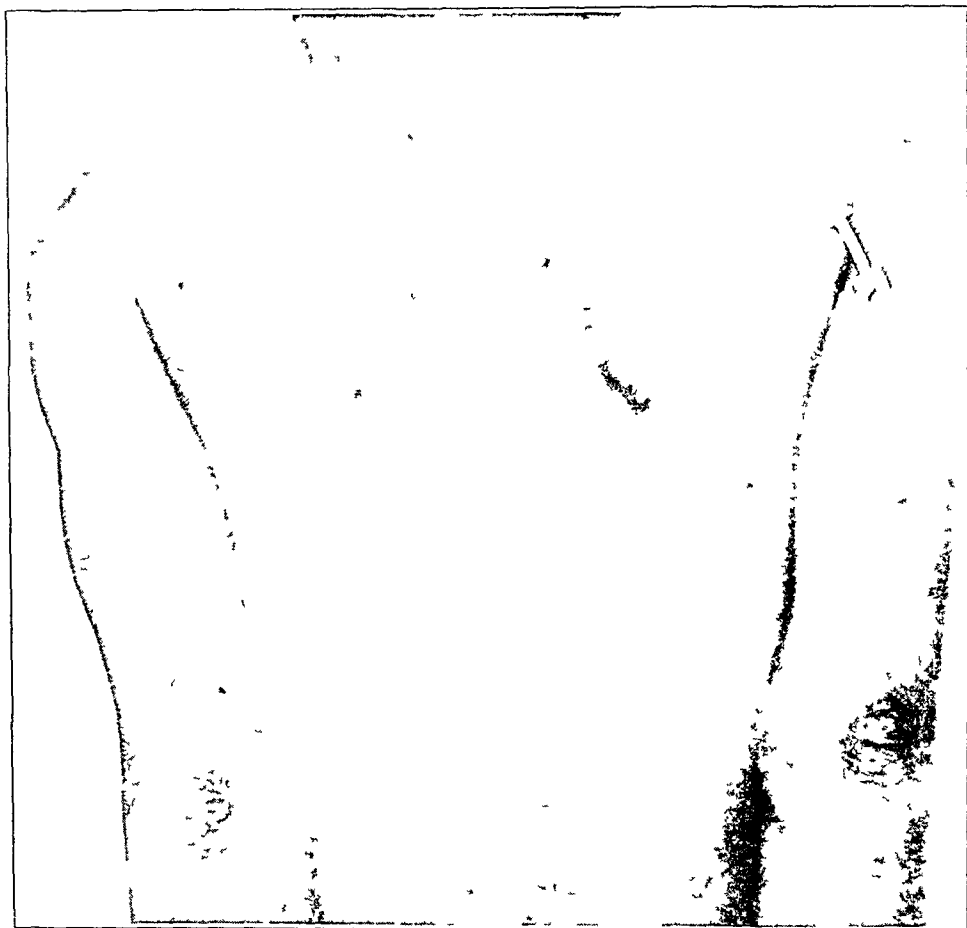


Fig 2 (case 1) —Lesions over the regions of the elbows The arrow points to atrophy of the muscles of the shoulder girdle



Fig 3 (case 1) —Patches over the small joints of the hands The arrow points to a characteristic lesion over one of the metacarpophalangeal joints Atrophy of the interosseous muscles can be seen

palpated in both axillas. The tip of the spleen could be felt on deep inspiration. The interosseous muscles and the thenar and hypothenar eminences were markedly wasted, however, there was no reaction of degeneration, stimulation with the electric current giving results within the range of normal. A blood culture was sterile for ordinary bacteria and for the tubercle bacillus. A specimen of stool showed no blood. The hemoglobin content was 76 per cent, the white blood cell count was 4,900, with 44 per cent lymphocytes. The blood pressure was 120 systolic and 48 diastolic. The temperature curve was subfebrile, a remarkable feature being the patient's unawareness of his fever. At one time it was believed that there was a short presystolic rumble at the apex of the heart, accompanied by some accentuation of the second pulmonic sound. These findings considered in conjunction with a snapping first sound at the apex, splenomegaly, lymphadenopathy, leukopenia and fever, were deemed suggestive of the Libman-Sacks group.

About two weeks after the initial observation, the patient complained of vagrant articular pains, but there was no demonstrable gross evidence of disease in the articulations. A few small, whitish patches, nonulcerated and slightly elevated, were observed in the buccal mucosa. The Pirquet and Mantoux tests were negative. There were moderately diffuse erythematous swellings of both upper eyelids. About a week later the patient had an attack of pallor in the distal phalanges of the fingers, which simulated the asphyxial stage of Raynaud's disease, pressure on the affected parts left bloodless areas for an abnormally long time. It was now learned that he had suffered several such attacks during the antecedent few months. Examination of several urinary specimens revealed no abnormal findings beyond the occasional presence of a few white blood cells. There was no evidence of renal impairment, the urea nitrogen content of the blood being 12 mg per hundred cubic centimeters and the concentrating power of the urine being normal. The blood calcium content was diminished, the values ranging between 8 and 9 mg. A roentgenogram of the chest disclosed no abnormalities. An electrocardiogram revealed only slight left axis deviation. A specimen of skin from one of the lesions on the knuckles showed, on microscopic study, marked hyperkeratosis, some edema and vacuole formation in scattered areas of the basal layer of the epidermis, as well as dilated blood vessels in the papillary bodies, and an infiltration of round cells about the blood vessels and in the adjacent parts. Sections were not stained for elastic tissue. Histologic examination of an axillary gland disclosed a nonspecific hyperplastic lymph node. Chemical examination of urine showed the qualitative presence of lead by a method in which positive results were considered to indicate abnormal amounts of the metal. Another such analysis made two months later was also positive. At no time had there been noted stippling of the red blood cells or other classic evidence of lead intoxication.

During the following two years the disease continued to run a subfebrile course though the patient remained unaware of the fever. He complained of generalized weakness, and there had been a loss of over 50 pounds (22.7 Kg) in weight. There was bilateral atrophy of the muscles of the shoulder girdle, the course of this condition being progressive. On several occasions there occurred a widespread purpura of the skin and the oral mucosa, associated with peculiar necrotic, slowly healing lesions on the legs and shoulders. Platelet counts revealed no abnormal changes. The other cutaneous patches remained unchanged, except that the flush area of the face was slightly more pigmented. The patient's sense of weakness seemed to be intensified by inability to use the hands. About six weeks before death, evidence of a "sclerodermic" process appeared on the face.

in the form of bilateral thickenings in the cheeks (edema of the skin and subcutaneous tissues?), rendering mobility of these parts difficult and interfering with smiling. The patient died at home as a result of pneumonia after an eventful course of some three years, during which time a variety of diagnoses had been suggested.

COMMENT ON CASE 1

1 *Cutaneous Features*—The occurrence of an erythema of the face, which assumed a "butterfly" configuration and which was subsequently replaced by pigmentation, the attributes exhibited by the lesions in the ears and in the oral mucous membranes, as well as the peculiar constitutional symptoms, appeared to be consistent with the clinical diagnosis of systemic lupus erythematosus. The initial impression of dermatitis venenata, based on the history of contact with chemicals, was a reasonable hypothesis, but it failed to take into account the systemic features, in a few other cases coming under my observation the early stages of disseminated lupus erythematosus were likewise attributed to contact with chemicals on the face (women) or on the hands (men). The pathologic alterations seemed to differ from those occurring in the average case of discoid atrophic lupus erythematosus, but the changes could be considered as similar to those observed in cases of the superficial varieties of that disease, notably the types accompanied by systemic reactions^{1b}. On the other hand, all the lesions noted were not unlike those encountered in typical examples of dermatomyositis, though in this case the painful, edematous muscular swellings generally observed in the latter condition were lacking. Of special interest was the presence of smooth, atrophic, glistening oval patches over the finger joints, these lesions were declared by Gottron to be characteristic, it not pathognomonic, of dermatomyositis, especially in its chronic stage. In 1931 I observed the appearance of a similar anomaly (case 2) in a patient whose condition was diagnosed as "exanthematic" lupus erythematosus and who also had marked muscular atrophy. Since then, other similar cases have come under my observation. It may be stated, then, that this type of eruption seems to be associated commonly with evidence of disease in the muscles, this subject will receive more detailed consideration in another publication. Finally, it is interesting to note the appearance of the peculiar thickenings in the cheeks observed in this patient a few weeks before death, the attributes of these patches simulating "scleroderma". It is my belief, however, in the absence of substantiating pathologic evidence, that the firmness of these areas was caused by an unusual localization of edematous fluid in the involved parts (subcutaneous, probably also cutaneous), a condition capable of

3 Gottron H. Hautveränderungen bei Dermatomyositis in *Comptes-rendus du huitième Congrès international de dermatologie et de syphilologie*, Copenhagen, 1930, p. 826

complete restitution to normal. This was demonstrated in case 5 (to be reported later in this paper), in which an almost identical phenomenon was encountered.

2 *Atrophy in the Muscles*—This feature was probably dependent on "primary" disease in the muscles rather than on initial involvement of nerves. The failure to obtain a reaction of degeneration favored this view, although it appears that too much reliance cannot be placed on responses to the electric current. I have also encountered atrophy of the small muscles of the hands in several examples of typical systemic lupus erythematosus, in these cases the clinical features did not in any way suggest the possibility of dermatomyositis. Of particular interest in case 1 was the subsequent development of atrophy in the muscles of the shoulder girdle, a phenomenon observed far more often in instances of dermatomyositis. It must be stressed, however, that at no time during the course were there painful, edematous swellings involving the musculature. Noteworthy was the marked loss of weight, over 50 pounds (22.7 Kg) in one year, this feature has been commonly encountered in dermatomyositis.

3 *Miscellaneous Features*—Additional points of interest in case 1 were (1) a leukopenia and relative lymphocytosis, which occur more commonly in systemic lupus erythematosus, occasionally in dermatomyositis and sometimes in lead poisoning, (2) a febrile state of which the patient was oblivious, (3) a low content of blood calcium, ranging between 8 and 9 mg, the significance of which is, however, unclear, and (4) enlarged axillary glands, showing on histologic examination only the changes of a nonspecific hyperplastic condition.

4 *Etiologic Considerations*—Study of the composite clinical picture suggested the possibility of a low grade, chronic, infectious process as the underlying basis of the symptoms, yet no evidence to substantiate this view was forthcoming, and the bacteriologic investigations proved fruitless. On the other hand, the onset of symptoms after the handling of chemicals, particularly lead, might have been justifiably regarded at first as coincidental, especially in the absence of classic evidence of plumbism, such as Burton's line, stippling of the red blood cells, colic, constipation and encephalopathy. Nevertheless, absorption of lead may be freely granted in view of its detection by urinalysis on two occasions two months apart, these findings were regarded as significant owing to the use of a relatively insensitive method for its isolation. In addition, the atrophy in the small muscles of the hands (Duchenne-Aran type) and the subsequent involvement of the muscles of the shoulder girdle might have been considered as suggestive evidence of plumbism. Definite criteria for the differentiation of lead intoxication from lead absorption

have been set down by Aub and his co-workers,⁴ but it must be admitted that the subject is still in a state of flux, especially in regard to the incipient, mild and atypical examples of this condition. The part played by idiosyncrasy is well recognized in classic instances of the disease, but little is known about its relation to other variants of the clinical picture. Even authentic cases of lead intoxication may occur in the absence of such features as basophilic stippling and discoloration of the gum line, if not permanently, at least temporarily.⁵ I have notes on one undoubted example of lead encephalopathy in which chemical examination of urine failed to reveal the presence of this heavy metal, and there are similar cases recorded in the literature. The interesting observation⁶ that a period as long as twenty years may elapse between exposure to the metal and the appearance of symptoms of plumbism can be correlated with the deposition of lead in the bones (probably in the form of tertiary lead phosphate), from which site it may be liberated into the blood stream by a series of propitious circumstances. If, on the one hand, it seems reasonable to believe that this heavy metal may enter the body by devious means and that it cannot be blamed for all the ills flesh is heir to, it seems, on the other hand, equally prudent to inquire into its possible relation to the onset or accentuation of obscure clinical pictures ordinarily not attributed to it. The following discussion will be concerned with certain suggestive evidence indicating (1) that lead may possibly play a part in the production or accentuation of conditions similar to that in case 1 and (2) that this may possibly be caused by a pathologic effect on the smaller blood vessels in the body.

In a remarkable monograph on lead poisoning, Aub and his co-workers⁴ summarized critically the evidence on the relation of this heavy metal to vascular disease. These investigators were unable to accept such a relationship, as they felt that no one had satisfactorily established proof of specific lesions in the blood vessels. Nevertheless, there are data pointing toward lead as a vascular poison in susceptible persons, though it seems probable that pathognomonic or even highly characteristic, pathologic changes are not produced. Zadek⁷ stated "Lead belongs to the few vascular poisons of which the mode of action is known. On the basis of numerous clinical, anatomic and experimental observations in animals, we know that lead attacks the vessels, especially the arterioles and capillaries, causing in time a hypertonic (generalized)

4 Aub J C, Fairhall L T, Minot, A S and Reznikoff, P. Lead Poisoning, Baltimore: Williams & Wilkins Company, 1926.

5 Linenthal, H. The Early Diagnosis of Lead Poisoning, *J A M A* **62** 1796 (June 6) 1914.

6 Waterfield, R L. A Case of Delayed Lead Poisoning with a Latent Period of Twenty-Four Years, *Guv's Hosp Rep* **81** 374, 1931.

7 Zadek, E. Zur Klinik der chronischen Bleivergiftungen, *Ztschr f klin Med* **116** 241, 1931.

arteriosclerosis" Teleky⁸ expressed the opinion that "vascular damage may be and remain the solitary sign of poisoning" Fishberg⁹ declared that "preeminent among the exogenous poisons which cause chronic hypertension in man, if indeed, there are any others, is lead," and he attributed this effect to "the vasoconstricting action of the metal on the arteries and, perhaps, the capillaries" According to Fishberg, there appears to be suggestive evidence that lead encephalopathy and colic are caused by vasoconstriction of the cerebral and mesenteric vessels respectively, these transitory episodes being designated as "vascular crises" in the sense of Pal

There are many conditions, at present classified as clinicopathologic entities, in which the vascular system is alleged to be the principal or predominant site of attack Among these may be mentioned arteriosclerosis (arteriolosclerosis),¹⁰ malignant nephrosclerosis,¹¹ periarteritis nodosa,¹² dermatomyositis,¹³ systemic lupus erythematosus,¹ Raynaud's syndrome¹⁴ and a few others not pertinent to this discussion As a rule these conditions may be differentiated from one another by the nature and extent of the pathologic changes, the size of the vessels chiefly affected and clinical pictures that are distinctive in most instances They are often conveniently classified under the generic heading of "diffuse vascular disease," this general term may, perhaps, represent an advance in conception, but it gives no hint at cause or the finer clinical differentiations, and its employment in nomenclature must not be allowed to degenerate into a veritable shibboleth The possible relation of some of these conditions to lead absorption and intoxication will be reviewed in the ensuing paragraphs

(a) Renal Vascular Disease According to Fishberg,⁹ the renal changes attributable to lead are definitely those occurring in the arteriosclerotic (vascular) kidney Brogsitter and Wodarz,¹⁰ in 8 cases, and Fishberg,⁹ in 2 instances, observed marked hypertrophy in the media of the small renal arteries, among other alterations in the vessels of that organ The article by the former investigators carries a list of

8 Teleky, cited by Zadek⁷

9 Fishberg, A M Hypertension and Nephritis, ed 3, Philadelphia, Lea & Febiger, 1934

10 Brogsitter, A M, and Wodarz, H Nierenveränderungen bei Bleivergiftung und Gicht, *Deutsches Arch f klin Med* **139** 129, 1922

11 Volhard, F, and Fahr, K T Die Brightsche Nierenkrankheit, Berlin, Julius Springer, 1914

12 Keil, H The Rheumatic Subcutaneous Nodule and Simulating Lesions, *Medicine* **17** 357, 1938

13 Fahr, T Zur Frage der Polymyositis (Dermatomyositis), *Arch f Dermat u Syph* **130** 1, 1921

14 Lewis, T The Blood Vessels of the Human Skin and Their Responses, London, Shaw and Sons, Ltd, 1927

the earlier recorded observations concerned with this relation. In many instances, also, the changes of arteriolar necrosis have been reported, for example, of the 36 patients with "malignant nephrosclerosis" (so-called combination form) studied by Volhard and Fahr,¹² 4 had worked in the lead industries, and 2 of these had previously shown evidence of plumbism. More imposing are the statistics furnished by Machwitz and Rosenberg,¹⁵ they observed that in a group of 36 patients with malignant nephrosclerosis containing 17 men, 9 of the men were lead workers. No case protocols were furnished by Volhard and Fahr, but in the single instance reported in detail by Machwitz and Rosenberg, the pathologic description of which is given by Lohlein,¹⁶ it is clear that the patient had been suffering from saturnism.

In addition to these changes in the arterioles, vascular alterations have also been noted in smaller blood vessels, including the capillaries of various organs.¹⁷ The changes were chiefly concerned with hyaline degeneration of the parietes accompanied in some instances by the formation of "hyaline thrombi," the pathogenesis of the latter phenomenon being variously interpreted. In most cases the description was limited to but a solitary organ, but when complete postmortem protocols were available it appears that the changes were more or less generalized in distribution. However, none of the vascular alterations seems to be pathognomonic of lead poisoning, but this conclusion need not negate the view relating to the effect of the metal on the blood vessels, the probable primary site of the disease. The evidence compiled appears to be too suggestive to be summarily dismissed on the ground of coincidence.

(b) *Dermatomyositis*. It is Fahr's¹³ belief that in many instances of dermatomyositis the initial, fundamental disturbances are in the blood vessels supplying the affected muscles, the alterations being a variant of "necrotizing arteriolitis," possibly allied to periarteritis nodosa. The fourth case¹⁸ to be described in detail in this paper showed evidence

15 Machwitz, H. and Rosenberg, M. Zur Klinik der "vaskulären Schrumpfnieren." *Deutsche med. Wchnschr.* **42** 1188, 1916.

16 Lohlein cited by Machwitz and Rosenberg.¹⁵

17 (a) Gaylor, J. Zur Histologie der Schrumpfnieren nach chronischen Bleivergiftung, *Beitr. z. path. Anat. u. z. allg. Path.* **2** 476, 1888. (b) Mott, F. W. Examination of the Nervous System in a Case of Chronic Lead Encephalitis, *Arch. Neurol. & Psychiat. Path. Lab., London* **4** 117, 1909. (c) Oller, J. N. Ueber hyaline Gefäßdegeneration als Ursache einer Amblyopia saturnina, *Virchows Arch. f. path. Anat.* **86** 329, 1881. (d) Eichhorst, H. Beiträge zur Pathologie der Nerven und Muskeln, *ibid.* **120** 217, 1890. (e) Freifeld, H. Zur Frage der pathologisch-anatomischen Veränderungen bei der Bleivergiftung, *ibid.* **268** 456, 1928. (f) Blackman, S. S., Jr. The Lesions of Lead Encephalitis in Children, *Bull. Johns Hopkins Hosp.* **61** 1, 1937. (g) Brogsitter and Wodarz.¹⁰

18 Karelitz, S., and Welt, S. K. Dermatomyositis, *Am. J. Dis. Child.* **43** 1134 (May) 1932.

partially substantiating this view. It is interesting that Fahr regarded lead as one of the possible factors in the production of changes grouped by him in the category of "necrotizing arteriolitis," this belief was in all likelihood based on his observation of similar vascular alterations associated with malignant nephrosclerosis, which, as stated before, had been encountered by Volhard and Fahr in 4 lead workers.¹¹

On the other hand, Schuermann¹⁹ recorded a typical example of dermatomyositis, the cause of which he attributed to the patient's exposure to lead. Perusal of this protocol will reveal a clinical course strikingly similar to that shown by case 1 in my report. In addition to that example there came under my observation, about seven years ago, another case of dermatomyositis that is eminently pertinent to this discussion. The patient in that case was examined some two months after she had been using a hair dye, the chemical composition of which was discovered only after her death. The clinical course was at first regarded as that of dermatitis venenata of the scalp,²⁰ but subsequently there were superimposed the features of dermatomyositis. The latter diagnosis was confirmed by postmortem examination performed some three months after the onset of the condition. Chemical analysis of the hair dye revealed only lead as the active ingredient. Despite the lack of classic evidence of plumbism, it seems probable that absorption of lead was a factor either in the production or in the accentuation of the illness, which ran an acute course, and this observation assumes greater importance in view of the data already discussed. It may be stated that this is a retrospective conclusion based on the results of a chemical analysis of the hair dye, these findings becoming available only after the death of the patient, it is possible that the ordinary evidence of plumbism was overlooked, though there was moderate secondary anemia.

(c) Systemic Lupus Erythematosus. The generalized nature of this disease has been discussed briefly in several other communications,¹ and it is probable that the distribution of dermatomyositis, too, is general. Relative to systemic lupus erythematosus, Ludy and Corson,²¹ studying specimens of skin by the spectroscopic method, observed appreciable amounts of lead in the specimens of 15 of 18 patients with systemic lupus erythematosus, the remaining 3 specimens showing faint traces of the heavy metal. In 20 specimens used as control material, the results were essentially negative in 17, while the remaining 3 (examples of vitiligo)

19 Schuermann, H. Zur Klinik und Pathogenese der Dermatomyositis (Polymyositis), *Arch f Dermat u Syph* **178** 414 1939.

20 This was probably an erroneous belief, as the features from the beginning were those of a case of originally unrecognized dermatomyositis.

21 Ludy, J B, and Corson, E F. Lupus Erythematosus. Increased Incidence Hematoporphyrinuria and Spectroscopic Findings. *Arch Dermat & Syph* **37** 403 (March) 1938.

revealed traces of lead. On the other hand, in 3 cases of lead poisoning spectroscopic examination of specimens of skin gave negative results. These findings are of fundamental interest, though it is difficult to be certain of the interpretation, in any event, substantiation of these data would be desirable before they are utilized generally. Ludy and Corson cited the record of Traub's patient,²² a painter, as tending to substantiate their findings, it is of great interest, therefore, to report that this reference concerns the patient whose history is now detailed as case 1 in my report.

(d) Absorption of Lead by the Skin and Other Cutaneous Phenomena. So far as the lead industries are concerned, absorption of the metal through the skin has been relegated generally to a minor position, if not entirely denied. There is, however, suggestive evidence that this may occur under certain conditions, with the production of symptoms of intoxication. Where the integument has been destroyed or its vitality impaired from any cause, absorption of lead has been freely granted, as in the instances recorded by Passler (eczema),²³ Gottheil (burn)²⁴ and Hahn²⁵ among others. The evidence on the question of absorption of the heavy metal through apparently intact skin is, however, more difficult to assess, in view of the opportunities for lead to gain access through the respiratory tract. There are a few such cases of intoxication, in which the patients used cosmetics containing this ingredient for many years²⁶ without having a dermatitis, but, as stated, the interpretation of these examples presents insurmountable difficulties, the modern opinion is that lead has been absorbed through the respiratory system. In any event, it is striking that in most cases the etiologic agent was discovered accidentally or only after amazingly long periods of observation.

22 Traub, E. A Case for Diagnosis (Lupus Erythematosus Disseminatus?), *Arch Dermat & Syph* **25** 562 (March) 1932.

23 Passler, H. Acute Bleivergiftung bei Ekzem nach Behandlung mit Diachylonsalbe, *München med Wchnschr* **41** 85, 1894.

24 Gottheil, U. S. Fatal Lead Poisoning from the Use of Burrow's Solution, *J A M A* **54** 1056 (March 26) 1910.

25 Hahn. Encephalopathia saturnina bei einem 13 monatlichen Kinde durch Hebräsalbe. Tod, nebst Bemerkungen über die Eclampsie, *Arch f Kinderh* **28** 172, 1900.

26 (a) Holland, J. W., in Peterson, F., and Haines, U. S. A Text-Book of Legal Medicine and Toxicology, Philadelphia, W. B. Saunders Company, 1904, vol 2, p 385. (b) Oliver, T. Lead Poisoning, New York, Paul B. Hoeber, 1914. (c) Robinson, G. W. Lead Poisoning from the Use of Cosmetics. Two Cases of the Neuromuscular Type, *J A M A* **64** 814 (March 6) 1915. (d) Sante, L. R. Lead Neuritis from Cosmetics, with Report of Two Cases, *ibid* **64** 1573 (May 8) 1915. (e) Woltman, H. W. Lead Poisoning from Face Enamel, *ibid* **79** 1685 (Nov 11) 1922. (f) Barron, M., and Haberm, H. C. Lead Poisoning, with Special Reference to Poisoning from Lead Cosmetics, *Am J M Sc* **162** 833, 1921. (g) O'Carroll, J. Saturnine Encephalopathy, *Dublin J M Sc* **95** 1, 1893.

The symptoms of plumbism have been explained largely on the basis of vasoconstriction of the blood vessels. The pains in the fingers, toes and perhaps also in the joints, which are often encountered in workers in the lead industries, have been attributed to vascular spasms. Similarly, it is possible that spastic constriction of the digital arteries may cause a clinical picture resembling Raynaud's syndrome, and, as this condition nearly always occurs in women, the observation of exceptional cases of its occurrence in men takes on added significance.²⁷ Among the exogenous poisons causing "symmetric angio-spastic gangrene," Curschmann²⁸ mentioned lead. It is interesting that Raynaud himself^{27a} encountered an instance of the syndrome in a lead worker who also had intermittent amblyopia. Cassirer^{27b} observed another instance in a man who had been exposed to the heavy metal and had previously manifested signs of saturnism. The observation of a Raynaud-like syndrome in case 1 in this paper seems interesting in this connection. Sainton's^{27c} patient, a painter, had several exacerbations of a condition like that in Raynaud's disease, after resumption of his occupation, and these attacks were accompanied by colic, the process went on eventually to gangrene of the affected parts. Timme's case^{27d} was especially noteworthy, as his patient had "obliterative endarteritis." In a subsequent communication, Timme^{27e} reported that the left foot of that patient had been amputated, that large amounts of lead were found in the muscle tissue and that "the cross section of one of the arteries showed obliterative arteritis with hypertrophy of the media, together with disappearance

27 (a) Raynaud, M. *New Researches on the Nature and Treatment of Local Asphyxia and Symmetrical Gangrene of the Extremities*, translated by T. Barlow, in *Selected Monographs*, London, The New Sydenham Society, 1888. (b) Cassirer, R. *Die vasomotorisch-trophischen Neurosen*, ed 2, Berlin, S. Krager, 1912. (c) Sainton, H. *Asphyxie symétrique des extrémités et menace de gangrène chez un saturnin*, *France méd* **1** 221, 1881. (d) Timme, W. *A Case of Endarteritis Obliterans*, *Boston M. & S. J.* **174** 539, 1916. (e) *Obliterative Arteritis and Lead Poisoning*, *Lancet* **2** 162, 1916. (f) Decloux, Ribadeau-Dumas, and Sabarcanu. *Localisations rares de la maladie de Raynaud*, *Presse méd* **10** 783, 1902. (g) Mader. *Angioneurosis spastica*, *Besserung*, *Jahrb. d. Wien. k. k. Krankenhäuser* **1** 668, 1892. (h) Kazda, F. *Gangran an den unteren Extremitäten bei Bleiarbeitern*, *Wien. klin. Wchnschr.* **36** 694, 1923. (i) Baader, E. W. *Beobachtungen an gewerblichen Bleivergiftungen auf der Abteilung für Berufskranke des Kaiserin Auguste Viktoria Krankenhauses zu Berlin-Lichtenberg*, *Opera collecta congressus medicorum internationalis pro artificibus calamitate afflictis aegrotisque Budapest* 1928, p. 411. (j) Lederer, E. *Bleigangran schwere, bei einem Glas-schleifer*, *Samml. Vergiftungs-fällen* **3** 115, 1932. (k) Rutishauser, E. *Bleigangran und Encephalopathie*, *Virchows Arch. f. path. Anat.* **297** 119, 1936.

28 Curschmann, H. *Raynaudsche Krankheit (Symmetrische angiospastische Gangrän)*, in von Bergmann, G., and Staehelin, R. *Handbuch der inneren Medizin*, ed 2, Berlin, Julius Springer, 1926, vol. 5, pt. 2, p. 1467.

of the media as described by Kolisko²⁹ Similar cases have been recorded by a number of other observers^{27,1,1}, in nearly all of them the attacks occurred during states of chronic plumbism In 2 unusual instances of disseminated obliterative arteritis recorded by Barker and his co-workers,³⁰ the factor of lead was regarded by them as coincidental, though in 1 instance there was definite evidence of a previous inter-current attack of saturnism, yet in the light of the data recorded in this paper it seems wise to reconsider the significance of this factor in relationship to these cases

On the basis of the data submitted, it seems probable that lead may act on the blood vessels in any of the three following ways, although there need be no specific changes in the pathologic appearance of these structures

1 It may have a direct action This presupposes a primary toxic effect on normal blood vessels

2 It may have an indirect action Vessels already affected for one reason or another may be further damaged Patients affected in such a manner need not show the classic evidence of lead poisoning In this respect the behavior of the heavy metal would be analogous to that of gold salts acting on the previously altered vasculature in cases of systemic lupus erythematosus¹

3 Lead may render the blood vessels more prone to damage from still other causes, such as exposure to cold

In studying this problem further, it must be determined more definitely (a) whether lead is indeed a vascular poison under exceptional circumstances, and (b) what its mode of action may be on presumably healthy and on previously altered blood vessels

REPORT OF CASE 2

In 1931 this case was presented before the Frankfurt Dermatologic Congress³¹ as an example of "exanthematic" lupus erythematosus This diagnosis was accepted without demur by a host of competent dermatologists Prof O Gans made it possible for me to observe the patient for over two months As there were numerous features of unusual interest

29 Kolisko, cited by von Schrotter L Erkrankungen der Gefasse, in Nothnagel, H Spezielle Pathologie und Therapie, Vienna, A Holder, 1901, vol 15, pt 3, sect 2, p 82

30 (a) Barker, N W, and Brown, G E Progressive Disseminated Obliterating Arteritis of Unknown Origin, M Clin North America **16** 1313, 1933 (b) Barker, N W, and Baker, T W Proliferative Intimitis of Small Arteries and Veins Associated with Peripheral Neuritis, Livedo Reticularis, and Recurring Necrotic Ulcers of the Skin, Ann Int Med **9** 1134, 1936

31 Seier Lupus erythematoses exanthematicus, Zentralbl f Haut- u Geschlechtskr **40** 175, 1932

and as the interpretation of the findings may provoke considerable debate, it seems desirable to outline the clinical aspects from notes taken during the early part of October 1931 and later.

When first seen by me the patient, a girl of 10 years, had already been in the hospital for almost one year. The illness began about November 1930, when there appeared a generalized rash, interpreted as scarlet fever. This was followed by sore throat, a hacking cough and vague pains in the body. At this time there were tense swelling and flaming redness of the left eyelids, accompanied two weeks later by a similar condition of the opposite eye, cheeks and knees, with pains in these parts. About Christmas of 1930, vesicles and bullae appeared on the knees and buttocks, these lesions resembled erythema multiforme exudativum. There was also a purulent discharge from the eyes, the nature of which remained obscure. At about this time the child was brought for consultation to the clinic of Professor Gans. The brief account by Seier²¹ stated that after the healing of bullous lesions, there appeared papular, partly confluent efflorescences showing atrophy and follicular hyperkeratosis, that at one time there was an acute exacerbation of the condition associated with flaming redness and swelling of the entire face, fingers and knees as well as "ulcerations" of the eyelids, that the tuberculin test was negative, and that the clinical picture resembled "sepsis" accompanied by bacterial endocarditis, "polyarthritis," edematous swellings of all the extremities and "polyneuritis." It is, however, only fair to note that there may be disagreement with this interpretation of the clinical features, and I therefore take this opportunity to interpolate additional notes with commentaries on the interpretation of the physical findings and the subsequent course.

The initial examination revealed enlarged inguinal, and a few small nuchal, glands. There was evidence of rhinitis. The mucous membranes were normal. The face was the site of a typical "butterfly" lesion, characterized by erythema, fine, adherent scaling, but no atrophy such as one is accustomed to observe in instances of discoid lupus erythematosus. The ears revealed a few scaling erythematous patches. The skin of the extensor aspects of the knees and elbows showed a symmetric disposition of bullae that had collapsed to form hemorrhagic crusts. There was erythema of the buttocks, with small interspersed areas of fine atrophy. At this point it seems important to stress the localization of erythematous, scaling, definitely atrophic lesions over the joints of the fingers on their dorsal aspects, an appearance recalling the attributes of the patches observed in case 1. In addition, the extremities were sites of acrocyanosis at their peripheries. The articulations showed no evidence of swelling. Physical examination of the heart and lungs revealed no abnormalities at the time. There was moderate secondary anemia and leukopenia on a few occasions. Several platelet counts gave normal figures. Early in the course several examinations of urinary specimens showed red blood cells and casts, the concentrating power of the urine was not determined. The temperature curve was at first high and fluctuating and was later subicubic. On one occasion frank hematuria appeared, but I subsequently ascertained that this had occurred about three weeks after the institution of therapy by injections of a gold salt. Furthermore, petechiae were observed and a tendency to thrombopenia but it was difficult to be certain whether this entire transient episode could be attributed to this medication, whether it represented an indirect exacerbation of "systemic lupus erythematosus" owing to superimposed damage to vessels already affected by the principal condition or finally whether these phenomena merely represented another manifestation of the disease itself. A roentgenogram of the chest disclosed no evidence of tuberculosis. Several cultures of blood were sterile.

except on one occasion when both a nonhemolytic streptococcus and *Staphylococcus aureus* were isolated (probable contamination?)

The patient was treated symptomatically with several transfusions of blood, and coincidentally the cutaneous lesions began to fade. An unusual feature, and the reason for the inclusion of the case in this report, was the occurrence of marked progressive atrophy of the muscles in the lower limbs, rendering movement of these parts difficult, if not impossible. The consulting neurologist attributed the condition to "septic polyneuritis," and a favorable prognosis was given. I was unable to agree with this opinion for reasons to be detailed under the general discussion of this case. The wasting of the muscles was apparently preceded by a stage of slightly painful edematous swellings of all the limbs, but the atrophy appeared chiefly in the musculature of the lower extremities, so that the child was unable to stand without the help of an attendant. For the relief of this condition she was placed under the care of an orthopedist. A curious feature was the unusual growth of hair on the forearms, a manifestation which is often mentioned in connection with cases of dermatomyositis and which I have encountered on several occasions.

Subsequently, cardiac murmurs were heard, and the diagnosis of endocarditis was therefore postulated. At this time the urinary sediment was free from formed elements. A tuberculin test was now positive and when repeated gave an even stronger reaction, however, the interpretation of these results remained speculative. At the time of the child's discharge from the hospital toward the end of 1931, the facial erythema was still visible in the form of red scaly lesions, especially over the upper eyelids, with similar symmetric patches over the knees and with peculiar areas of atrophy on the skin overlying the dorsal aspects of the joints in the hands. There were pronounced atrophy of the lower limbs and practically complete loss of power in these parts. The child was sent home, though one could hardly talk of cure, considering the state of the lower extremities. I later learned that the child became worse and was admitted to a hospital in a neighboring town.

COMMENT ON CASE 2

The clinical attributes of the eruption and the nature of the constitutional symptoms (such as fever, urinary findings, lymphadenopathy and exacerbation following injections with a gold salt) were consistent with the diagnosis of "exanthematic" lupus erythematosus, or subacute disseminated lupus erythematosus. The features exhibited by the dermatosis were considered so typical of this disease as to provoke no contrary opinion. Of particular interest were the atrophic patches in the skin overlying the joints of the fingers, these lesions recalled the ones observed in case 1. The most striking feature in the case was the diffuse muscular wasting of the lower extremities, which rendered the child paralytic. The neurologic opinion that this manifestation belonged in the category of "septic polyneuritis" was based on a doubtful interpretation of a single positive culture of blood in the face of several previous sterile results. It is my belief, however, that this condition was an instance of "primary" disease in the muscles of the lower limbs, showing the following characteristics:

- 1 Diffuse wasting of muscles. This was apparently preceded by a stage of edematous swelling in all the limbs, notably the lower ones.

2 Absence of severe pain The painful element was not striking at the time of my examination, and there was no evidence that pain had ever occurred in the standard distribution of the suspected nerves

3 A distribution of diseased muscles not in correspondence with that which one would expect from involvement of nerves alone Diminution of the deep tendon reflexes is by no means a differentiating feature

I have encountered subsequently a case of an almost identical condition in a child about 4 or 5 years of age There were puffiness and swelling about the eyes, a subfebrile course and progressive atrophy and paralysis of the lower limbs The occurrence of diseased muscle was substantiated by microscopic study of a biopsy specimen, and it was evident that the wasting condition had arisen and progressed in an insidious and painless manner In this case, also I noted peculiar erythematous, scaly and somewhat atrophic lesions over the small joints of the hands, a photograph of which will be found in a succeeding publication

It is reasonably certain that had stimulation with the electric current been carried out in case 2 a reaction of degeneration would have been absent Neurologists seem hardly to be familiar with this peculiar condition in its various and manifold phases In addition to the diagnosis of "septic polyneuritis," I have known conditions of this sort to be classified as progressive muscular atrophy pseudo-hypertrophic muscular dystrophy and, in the end stages as "scleroderma" Orthopedists are likely to observe these conditions in the chronic phases and to designate them as myositis fibrosa without realizing the relation to the early muscular phenomena occurring in typical instances of dermatomyositis Several years ago I observed the patient whose condition was described by Blau (case 1 in his report)³² under the title of myositis fibrosa In this instance also, there were the peculiar atrophic lesions over the phalangeal joints and there was a history of a previous condition that could be readily fitted into the clinical picture of a mild case of dermatomyositis (rash on the arms, a febrile course of several weeks, extreme weakness and persistent dysphagia) This case was originally regarded as one of poliomyelitis, a diagnosis often made in such instances The contractures about the large and occasionally the small joints are also often interpreted by neurologists and internists alike as manifestations of rheumatoid arthritis Of this syndrome I have encountered several striking examples in all these cases the significance of the cutaneous manifestations seemed to have been overlooked These instances are of wide interest for they shed light on the prognosis of

32 Blau A Primary Generalized Myositis Fibrosa Report of Two Cases with Histopathology J Mt Sinai Hosp 5 432 1938

this group of anomalies, but unfortunately the privilege of observing large numbers of these conditions in various phases of development is granted to but few. My own observations indicate strongly that these anomalies are far from rare.

The occurrence of hypertrichosis of the forearms is a feature commonly encountered in cases of dermatomyositis, according to my observations and others recorded in the literature. Its presence has led occasional investigators to suspect an endocrine factor. This possibility cannot be entirely negated, but it is my clinical impression that the increased growth of hair represents an effect of mild inflammatory stimulation caused by an antecedent erythema or by pathologic vascular changes in the subjacent subcutaneous and cutaneous tissues. This type of hypertrichosis seems to occur chiefly in areas in which there has been previous involvement of the blood vessels, of which redness and edema often represent the visible phenomena. Why this should occur in some patients and not in others and why this is not observed as commonly in other inflammatory processes implicating the integument, are questions to which our present knowledge fails to provide absolutely decisive answers. It is therefore a phenomenon worthy of further study.

Here, then, is another case illustrating features commonly observed in instances of both systemic lupus erythematosus and dermatomyositis. Many years ago Orzechowski³³ remarked that the diagnosis in such cases depends largely on who first sees the patient, the dermatologist or the neurologist. Case 2 also illustrates the futility of classifying such conditions as "cured," without an adequate system of follow up, whether it is personal or through the mediation of large clinics, for in this case, at least, I was able to ascertain that the patient had experienced another exacerbation of sufficient severity to warrant hospitalization.

REPORT OF CASE 3

The history of this patient, recorded by Davison³⁴ in 1929, presents many interesting features. An abstract of the most pertinent ones will be given, together with additional interpolated notes. It will be my purpose to show that the diagnosis could have been made ante mortem had more attention been paid to the peculiar nature of the cutaneous manifestations.

A woman aged 23 was first seen at the Mount Sinai Hospital on Sept. 3, 1925. In 1924 she had an attack of sore throat. Several months later she experienced vague pains in the extremities. According to Davison's detailed account, "the condition was first noticed in March 1925, when she observed three dark brown spots on her forehead and redness of the neck and chest. A few weeks

33 Orzechowski, K. Disseminierte chronische Myositis und Lupus erythematosus, *Arch f Dermat u Syph* **137** 369, 1921.

34 Davison, C. Dermatomyositis. A Clinicopathologic Study, Report of a Case with a Complete Necropsy, *Arch Dermat & Syph* **19** 255 (Feb.) 1929.

later she developed pains in both arms, and her face and feet became swollen (edematous) and painful. She sought the advice of a physician, and examination at the time showed a slight elevation in temperature, blowing systolic murmur at the apex and a rapid heart rate." About seven weeks before the first period of hospitalization, the tonsils were ablated. After this operation there occurred gradual progressive swellings of the legs and face, dyspnea, pains in the jaws and brownish pigmentation of the forehead. The patient complained of palpitation and precordial pain.

Physical examination showed an irregular area of brownish pigmentation on the forehead. There was considerable edema about the eyelids, with bluish discolorations especially evident on the right side. The face was puffy, the swelling being nonpitting. The physical signs heard on examination of the heart were interpreted as indicating chronic rheumatic cardiovascular disease (mitral stenosis and insufficiency), the subsequent postmortem examination showed these findings to be erroneous. The hemoglobin content was 65 per cent and the leukocyte count 6,800, with 64 per cent polymorphonuclears. The leukocyte count could be regarded as indicating relative leukopenia in view of the subfebrile course, the temperature occasionally reaching 100.2 F. Examination of urinary specimens revealed no abnormalities. The content of urea nitrogen was 12.6 mg. The basal metabolic rate ranged between +30 and +41, these results were, at least in part, attributed to the fever. The blood pressure was 102 systolic and 62 diastolic. Examination of the eyes showed no local lesion to account for the edematous lids, and the fundi appeared normal. There was no evidence of disease in the sinuses. It was suggested by some that this case might be one of acute lupus erythematosus. Others interpreted the regressing lesions about the eyes as those of a fading phenolphthalein eruption. "During this interval [about six weeks] she developed a stiff neck and was not able to move the head and shoulders in any direction, or raise the arms upward." This so-called "asthenia" was originally reported as of "psychic" origin. So far as other cutaneous manifestations are concerned, the record appears to indicate that they were absent, possibly overlooked.

From this time until her death in the latter part of 1926, the patient visited several institutions, finally reaching the Montefiore Hospital, where the diagnosis was arrived at on the basis of the findings at necropsy. For the remainder of the history and physical findings I am indebted to Davison's excellent report. In December 1925 the patient was admitted to the Presbyterian Hospital, where evidence of pulmonary suppuration was observed, for which bronchoscopy was performed. Finally, owing to a recurrence of the symptoms, she entered the Montefiore Hospital, where the following observations were noted. "Examination showed a white woman, undernourished, lying helplessly in bed, she was unable to sit up, and held the head rigidly with the arms at the sides. The skin of the head, neck, chest and upper arms showed a peculiar brownish pigmentation. There was some edema about the face and feet which did not pit on pressure. The sternocleidomastoid muscles could not be felt, and the head could not be supported alone. There was pain on pressure of the neck. The extremities showed a partial ankylosis of the shoulders and elbow joints with muscular wasting, more marked in the upper extremities. The arms could not be raised above the elbows, and the shoulders could not be raised from the pillow. The muscles of the thigh were weak, and painful on pressure. The electrical reactions showed a normal response in the muscles of the upper extremities. The platysma and sternocleidomastoid muscles did not respond to galvanism or faradism. There were no opening contractions." There was clinical evidence of pulmonary

suppuration, and the presence of this complication probably explained the increased white blood cell count (20,900, with 74 per cent polymorphonuclear leukocytes). The blood pressure was normal. There was no evidence of renal disease, aside from a few granular and hyaline casts in the urinary sediment. Roentgenographic examination of the extremities "disclosed moderately advanced arthritic changes of the right elbow, especially in the articular surface of the olecranon. There was slight periostitis along the upper third of the shaft of the radius. The right shoulder revealed slight arthritic changes and moderate amount of bone atrophy along the upper end of the shaft of the humerus." Throughout the course the fever was remittent.

Postmortem examination disclosed several findings that had not been stressed clinically. "The skin over the face and anterior surface of the neck was tense and smooth with a purple color" [superimposed postmortem lividity?]. The extremities showed slight but definite contractions at the elbow, wrist and interphalangeal joints. The overlying skin was thinned out, smooth and purplish over the fingers. The muscles were strikingly thinned out and pale." The other important findings were: in many muscles various degenerative changes, generally advanced (for example, fibrosis), generalized lymphoid hyperplasia (many lymph nodes enlarged, persistent thymus), bronchiectasis of the lower lobe of the left lung, terminal bronchopneumonia, and "contractures with atrophy of the skin of the extremities, face and neck."

COMMENT ON CASE 3

In this case the early history provides features of interest. The condition was diagnosed as acute disseminated lupus erythematosus, chiefly because there were erythematous swellings about the eyelids. The manner in which the lesions underwent gradual involution with the production of pigmented areas (indicating the previous presence of inflammatory changes) was strikingly illustrated by the diagnosis of "fading phenolphthalein eruption." The detailed history related by Davison³⁴ indicates clearly that early in the course the patient had noted painful edematous swellings of the face and lower limbs, and it is also clear that evidence of muscular atrophy was observed later in the upper extremities, with partial ankylosis resulting probably from the secondary effects of fibrosis. The reactions to the electric current were consistent with those of "primary muscle disease," rather than with primary involvement of the nerves followed by atrophy of the muscles, the former view seemed all the more reasonable since the tests were done more than a year after the onset of the condition. The post-mortem protocol noted certain changes in the skin, which recalled vaguely some of the features occurring in the eruptions in systemic lupus erythematosus and chronic dermatomyositis, the latter diagnosis was particularly likely in view of the changes in the integument overlying the joints of the fingers. The impression that the patient had rheumatic heart disease was not substantiated at necropsy, and it seems desirable to stress the point as these cases are often labeled as instances of rheumatic fever. Finally, the occurrence of generalized enlargement of the internal lymph nodes, which was reported by Davison as an

interesting observation, is a phenomenon that is commonly encountered in cases of systemic lupus erythematosus. It is likely that the occurrence of this manifestation will be recorded more often, commensurate with increasing interest in this phase of the disease, the occasional occurrence of necrotic areas in the enlarged lymph glands in instances of systemic lupus erythematosus has been often interpreted, on the basis of superficial examination and study, as evidence of a tuberculous source.

REPORT OF CASE 4

The patient whose case was reported in an interesting paper by Karelitz and Welt¹⁸ (1932) presented a number of dermatologic features that merit a more detailed consideration. Early in 1931 I carried on correspondence with the Massachusetts General Hospital, and on June 10, 1931 this institution furnished interesting notes which bear analysis and from which valuable lessons may be learned. In addition to information from these sources there will be appended a number of personal observations to complete the essential data abstracted from the report of Karelitz and Welt.

A girl aged 6 years became ill "about Aug. 4, 1929, when red streaks were noticed under both eyes. The areas of redness lasted one week, then spread lower down the face, crossing the nose and causing a butterfly-shaped erythema. Within two weeks there were marked anorexia and edema under both lower eyelids, the eruption spread over the extensor surfaces of all the extremities, and there were patchy areas on the buttocks. The diagnosis of lupus erythematosus was made, and ultraviolet ray treatment given, without any improvement. On Sept. 26, 1929, after increasing weakness, loss of weight, edema of the face and persistent cutaneous eruptions, the child was admitted to the Massachusetts General Hospital, where the diagnosis of lupus erythematosus was confirmed. A tuberculin test with a dilution of 1:1,000 was negative, and roentgenograms of the chest were suggestive of enlargement of the hilus gland." At this point the observations made in that institution may be introduced. There was a butterfly-shaped area of erythema extending across the nose onto the cheeks; the patch was smooth and slightly raised. There was some edema around the eyes and on the bridge of the nose. The skin about the elbows and on the extensor aspects of the arms had a blotchy, dusky red hue. There were symmetric similar areas on the buttocks as well as on the knees and shins. With the exception of one feature to be mentioned in the discussion, the eruption was suggestive of acute disseminated lupus erythematosus. A roentgenogram of the chest revealed the following abnormal condition: The hilus shadows were somewhat increased in density, and the larger lung markings were prominent, especially those running in the left upper portion of the chest; findings were consistent with hilus tuberculosis. There was no evidence of parenchymatous involvement of the lung. In the discharge note, dated Oct. 15, 1929, the condition was classified as lupus erythematosus. It was recognized that though the roentgenographic report stated that the picture was consistent with hilus tuberculosis there was no clinical evidence, and the tuberculin test, with a dilution of 1:1,000 was negative. In view of the tuberculous hypothesis of lupus erythematosus prevalent at the time, care in a sanatorium was advised. Up to this time there had been no symptoms pointing definitely toward involvement of muscles.

On her arrival at home, "the child first complained of being tired and unable to walk" The face showed edematous involvement, which extended over the entire body "On October 22, the patient began to have a daily temperature of 99 F in the morning and 101 F in the afternoon Gradually she became unable to move and cried with pain on being moved A diagnosis of acute rheumatic fever was made " and salicylate therapy in large doses was administered "The condition remained unchanged until about December 1, when her pulse rate suddenly rose from 100 to 120 to 160 to 180 A systolic murmur was heard, and several days later a diastolic murmur became audible A cardiologist then concurred in the combined diagnosis of lupus erythematosus diffusa and acute rheumatic fever with endocarditis About December 20 the temperature began to rise to 103 F daily, despite the large doses of salicylates" On December 29, the patient was seen by Dr Karelitz in consultation He observed that at this time "there was a red erythema, butterfly shape, over the face and nose, and irregular over the dorsal aspects of the arms, elbows, wrists, thighs, knees, legs and ankles The eruption was scaly and itched, it healed under the eyelids, leaving white areas of depigmentation The edema was firm, indurated and brawny, and in places, doughy There was no pitting The child lay immobile, with marked tenderness on pressure or passive motion She could not move any part of her body, except her face, without pain Her forehead was deeply pigmented brown the heart was not enlarged, the pulse rate was 140, and there were a soft systolic and a faint diastolic murmur at the apex The urine was normal and the blood count was normal except for 5 per cent eosinophils A diagnosis of dermatomyositis was suggested as the only possibility that might explain the entire clinical picture and history

"The patient was admitted to Mount Sinai Hospital on Jan 9, 1930, about the beginning of the sixth month of her illness" On examination it was found that the clinical picture had undergone some changes in that "the edema was less marked, some of the cutaneous lesions had improved [leaving residual areas of pigmentation], and the child could move her toes and fingers Ulcerations in the inguinal folds and over the internal malleoli [previously noted] had healed The temperature was 101.8 F, the pulse rate 120 and respiration 28" Examination of the heart revealed only a systolic murmur at the apex, which lacked the attribute of transmission The edge of the spleen was palpated by some observers I noted enlarged lymph nodes in the axillas, but these did not become more pronounced subsequently The extremities showed some muscular atrophy There was considerable hypertrichosis over the forehead and the upper and lower limbs, the patient's mother stated that this feature had become more marked since the inception of illness Laboratory reports showed that the Wassermann test was negative, that there was moderate secondary anemia (hemoglobin content, 72 per cent), that there was a striking leukopenia of 4,700 white blood cells, with 67 per cent polymorphonuclears and 9 per cent eosinophils, that the urinary specimens, aside from a faint trace of albumin and occasional white blood cells in the sediment, were free from abnormalities, that there was no evident impairment in renal function, the content of urea nitrogen in the blood and the concentrating power of the urine being normal, that the blood pressure was 114 systolic and 70 diastolic, that the Pirquet and Mantoux tests (up to 10 mg of old tuberculin) were negative, that the specimens of stool showed no ova or parasites to explain the eosinophilia, and that various roentgenographic examinations (including those of the heart, lungs, sinuses and other parts) disclosed no abnormalities Of interest was the unexplained increase in the amount of blood calcium (12.4 mg)

The nature of the rash was variously regarded. On one occasion the diagnosis of lupus erythematosus was eliminated owing to lack of definite evidence of atrophy in the lesions. At another time the sudden appearance on the extensor aspects of the ankles and feet of an irregular, blotchy, violaceous eruption hemorrhagic and nummular, which did not fade on pressure, was regarded simply as telangiectasia but the formation of definite telangiectatic rings enclosing apparently healthy centers, perhaps slightly depressed (?), produced a decided resemblance to Majocchi's disease (purpura annularis telangiectodes).

"A biopsy of the biceps muscle performed January 16 showed the typical picture of dermatomyositis: atrophy of the skin, edema and fragmentation of the muscle fibers, loss of striation, fatty degeneration, round cell infiltration and perivascular infiltration around the small vessels." It is interesting that the "electrical reactions of the muscles were normal, the cathodal closure being greater than the anodal, there was prompt response to the faradic current."

On January 28 the skin about the eyes showed a pale erythematous discoloration with superimposed formation of definite telangiectatic vessels. This was followed by similar involvement in the integument overlying the joints of the hands. Subsequently, the facial erythema became more pronounced, assuming again the typical "butterfly" configuration occurring in lupus erythematosus, accompanied by an intensification in the lesions over the upper eyelids and the appearance of an eruption over the upper part of the chest. The dermatosis was designated by another dermatologist as telangiectasia of the cheeks, chest and knuckles. It was also noted that erythematous and telangiectatic lesions would appear on the abdomen at sporadic intervals, and the same anomaly occurred on the dorsal aspects of the hands, notably over the joints, the areas varied in size from that of a pinpoint to that of a finger nail. Finally, about three weeks before death, another observer suggested the diagnosis of lupus erythematosus disseminatus of telangiectatic type; this opinion was based on the presence of dusky red, purplish patches on the face and dorsum of the fingers, the lesions showing slight fine scaling and small areas of what was interpreted as incipient, though definite, atrophy. The diversity of opinion was explained by the remarkable variations in the appearance of the lesions from time to time.

"The child gradually was able to move her arms enough to feed herself and when propped up in a sitting position could bend her knees but not abduct or rotate her thighs. The temperature dropped to normal but fever recurred off and on for one or more days." The patient was treated symptomatically by diverse methods, without striking or apparent benefit. It is of great interest that exposures "to infra-red and ultraviolet rays and to massage at times caused exacerbation of fever. Several decubitus ulcers developed on the back and some ulcerations in the axillae. These lesions did not heal under the usual treatment and the patient died [April 13, 1930, or about eight months after the onset of illness] with a terminal bacteremia," the temperature rising to 106.5 F and a blood culture showing *Streptococcus hemolyticus*. However, bacteriologic examinations had prior to this time been sterile.

"The postmortem diagnosis was dermatomyositis, acute septic enterocolitis, decubitus ulcers, hypostatic congestion of the lungs, and several other conditions. Two striking features in the pathologic condition were the involvement of the musculature of the blood vessels and the intestinal ulcerations." An excellent illustration of the vascular changes which were believed to be distributed as shown in figure 3 in the report by Karcher and Weil.

COMMENT ON CASE 4

As the diagnosis of acute disseminated lupus erythematosus was suggested on a score of occasions, it is evident that the early cutaneous lesions showed striking similarities to that condition. The difficulties in differentiating that disease from dermatomyositis were then considerably enhanced, as there was apparently no clinical evidence of involvement of the musculature. It is probable that the initial appearance of an eruption about the eyes, with subsequent spread to the flush area of the face, is a feature pointing toward the diagnosis of dermatomyositis. In the average case of systemic lupus erythematosus the areas of the eyelids, especially the upper ones, are occasionally involved, but this usually occurs as a secondary spread from an intensified process in the cheeks, there are, however, a few exceptions to this rule. The clinical significance of this phenomenon as well as of the cutaneous lesions over the joints of the fingers has been briefly indicated and will be discussed at length in another publication.

It is also interesting that there were exacerbations of fever after the therapeutic application of ultraviolet irradiation, a response that is commonly observed in the average example of systemic lupus erythematosus. That a similar phenomenon is encountered in dermatomyositis is indicated by a steadily growing literature devoted to this phase of the subject. Here it suffices merely to take cognizance of this fundamental behavior. The practical application of the fact immediately suggests itself and needs no further comment.

The normal reactions to the electric current in this case were consistent with the belief that the muscular involvement occurring in dermatomyositis and related states is, in all likelihood, a primary one rather than the secondary result of involvement of the nerves. The latter view has been suggested in connection with cases characterized by much pain and pronounced atrophy of muscular tissue, but it appears that these symptoms may be explained more satisfactorily on the basis of the former hypothesis. The term "primary muscular disease" does not necessarily eliminate the part played by the alterations in the blood vessels, and, indeed, there is evidence indicating that in many cases of dermatomyositis the fundamental process occurs in the vasculature, with secondary implication of the muscular parenchyma.

The preliminary diagnosis of rheumatic fever was not corroborated post mortem. This point is stressed, as "rheumatism" is regarded by Fahr¹³ as one of the etiologic factors in conditions characterized by "necrotizing arteriolitis", neither the presence of pains in various parts of the body, including the periarticular portions of the joints, nor the pathologic evidence of vascular changes of the type just mentioned is pathognomonic of rheumatic fever as defined in its strict sense, the results of numerous postmortem examinations also speak clearly against that view which would make of dermatomyositis a rheumatic disease.

While hesitating therefore to disagree with so eminent an authority as Fahr, I think it probable that this is one of the few times when this investigator has employed the term "rheumatism" in an obscure sense.

Of equal importance was the implied diagnosis of hilus tuberculosis and the suggestion that the patient be segregated in a sanatorium. This opinion was based on a doubtful interpretation of a roentgenogram of the chest and the occurrence of an eruption diagnosed as lupus erythematosus, the supposition being that this rash indicated a tuberculous source. The consistently negative tuberculin tests, later in high dilutions, and the absence of active tuberculosis post mortem, despite a progressively severe course, are points that appear to eliminate satisfactorily this theory of cause. It has been pointed out that the evidence based on studies at necropsy is at variance with the hypothesis relating lupus erythematosus to tuberculosis directly and that the association is generally "coincidental and unrelated." There are, however, reasons for believing that in exceptional cases there may be an indirect relation, a stirring up of tuberculosis in lymph nodes which have been the former sites of this disease. In any event, it is clear that in case 4 there was no evidence of tuberculosis.

Likewise, no etiologic conclusions can be drawn from the observation of *Streptococcus haemolyticus* in a culture of blood taken just before the death of the patient, as it was probably the result of an invasion from a sacral decubitus ulcer. As previous bacteriologic investigations had been fruitless, it is likely that this represented an intercurrent complication prematurely closing the course.

REPORT OF CASE 5

The patient in this remarkable case was observed at the Svidenham Hospital in the service of Dr. I. Jesse Levy and was first seen by me through permission of Dr. A. Rostenberg, Sr. From the beginning the condition was recognized as peculiar, and, despite opportunity for subsequent study, no unified opinion was reached. It is my belief, however, that the clinical features were those of dermatomyositis of an acute type with associated findings that suggested peritonitis nodosa. The initial fulminating character of the condition and the surprising recovery that apparently ensued were remarkable though the latter was followed by a transient relapse.

The patient, a 14-year-old boy born in the United States but of Spanish descent, was first observed on April 6, 1937. About one week before his admission there appeared a few reddish, painful swellings on the skin gradually spreading to other portions of the body. He also complained of fever, chills and a headache. Shortly after he noticed that the voided urine was red. He had an eye sore there and swallowing was difficult. The eyelids and forehead became swollen and he complained of severe pains in the limbs. There was no appreciable rise in temperature, no rheumatic fever or scarlatina.

On his admission a physical examination was carried out with difficulty, owing to the excruciating pain experienced by the patient on turning from side to side and on being touched. He appeared acutely ill. Examination of the heart revealed a tachycardia (140 beats in a minute), no murmurs were audible. The liver and spleen could not be palpated. The abdomen was neither rigid nor tender at this time. The face and all the limbs were sites of erythematous swellings which were warm to the touch and exquisitely tender, and which apparently involved the subcutaneous tissues as well. Among the diagnoses offered were multiple abscesses with bacteremia, acute rheumatic fever, periarteritis nodosa and acute bacterial endocarditis.

On April 7 a peculiar edema and redness of both the infraorbital and the supraorbital region were observed. The erythema extended down to the region of the nose, but the distribution did not precisely resemble that seen in the "butterfly" rash of lupus erythematosus. The movements of the eyeballs were normal, examination of the ocular fundi revealed no abnormalities. The throat was somewhat reddened, but no exudate was visible, a smear, however, showed pus cells and diplococci, and a culture revealed a pure growth of *Str. haemolyticus*. The temperature fluctuated between 101 F and 103 F. On several occasions the urine was frankly hemorrhagic, and from the beginning examination of such specimens showed many red blood cells, white blood cells and occasional hyaline and granular casts. Analysis of the blood revealed hemoglobin content, 63 per cent, red blood cell count, 4,280,000, white blood cell count, 54,600, with 93 per cent polymorphonuclear leukocytes. The content of urea nitrogen was 40.3 mg, indicating a moderate degree of azotemia. Other observers now felt that this was a case of acute lupus erythematosus.

On April 8 the outstanding feature was the presence of "nodular" thickenings distributed over various parts of the body, notably the limbs, these indurations were reddish blue and tender, and seemed to involve skin, subcutaneous tissue and muscle. The submental and left axillary glands were moderately enlarged. Because some of the cutaneous lesions had a purplish hue, it was believed that hemorrhage was present, and on this basis the suggestion of Henoch's purpura was advanced. A culture of blood, taken on admission, was now reported as sterile. Among the other diagnoses offered were acute periarteritis nodosa, dermatomyositis and erythema nodosum.

On April 9 several erythematous areas showing various attributes were observed. About the eyes, forehead and right forearm there were erythematous lesions that were not well demarcated. Over the upper aspect of the right thigh and on the right foot were two large, roughly oval patches with circumscribed, raised borders and relatively depressed centers, in the latter areas the skin felt taut and slightly indurated (edema?). Owing to the excruciating pain, a complete examination could not be carried out.

Several days later I saw the patient for the first time. The skin of the forearms, legs, thighs and feet revealed roughly oval and margined patches, the dimensions of which ranged from 2 inches (5.08 cm) to about 4 inches (10.16 cm) in their longest diameters, the borders were erythematous, raised and irregularly contoured, whereas the centers were relatively depressed, though level with the surrounding skin, were brownish blue in some areas and paler in others and were edematous and somewhat tender when pinched or even when gently touched. How much of the tenderness was actually resident in the skin itself it was difficult to determine, for the effect of even slight manipulation was transmitted to the underlying structures, which were manifestly sensitive to pressure. A few erythematous, irregular

patches were observed on the integument overlying several knuckles and some of the phalangeal joints. The eyelids were puffy and discolored a reddish brown, the appearance and the clinical course differentiating these lesions from angio-neurotic edema (fig 4). The muscles of the limbs, especially the large bundles, were markedly swollen and painful to touch, pressure on the large muscular masses of the upper limbs revealed pitting edema, and it seemed probable that the subcutaneous fat was also implicated in the process. A few small, erythematous lesions capped by a whitish membrane were found on the buccal mucosa. Another culture of blood was sterile. In the interim, also, the anemia had become more extreme in the course of a few days. The hemoglobin content fell to 25 per cent, the red blood cell count was 1,320,000, the platelets numbered 370,000, the white blood cell count was 78,000 with 87 per cent polymorphonuclear leukocytes, of

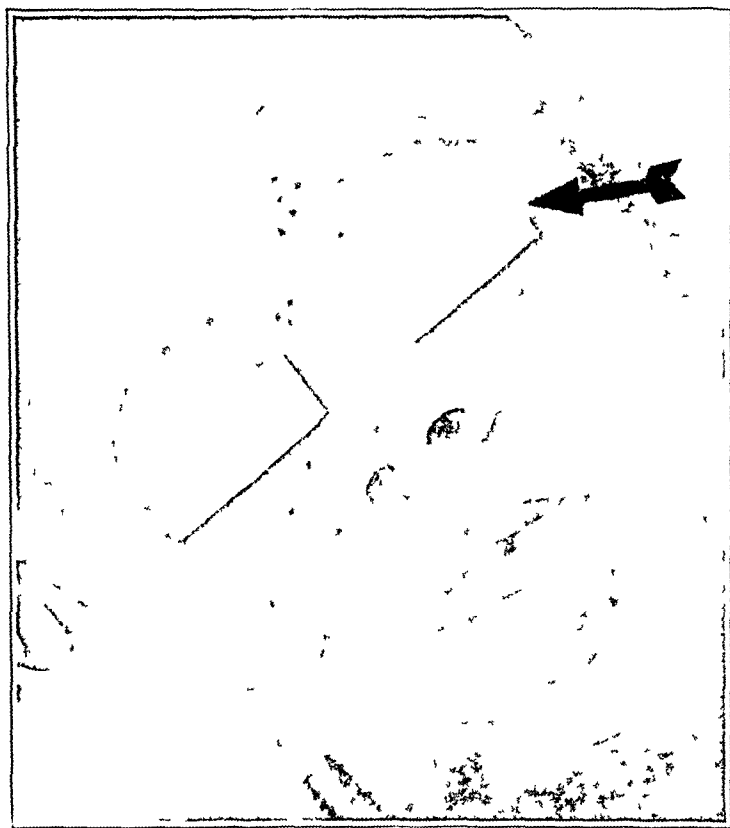


Fig 4 (case 5)—Discolored areas of edema involving the eyelids. The remainder of the eruption is acne vulgaris.

which about half were immature forms. The clinical picture was consistent with the diagnosis of dermatomyositis, however, the gross hematuria, the formed elements in urinary specimens, the moderate azotemia and the unusually high leukocyte count were features suggesting periarteritis nodosa. It may be parenthetically added that gross hematuria has been found in occasional instances of dermatomyositis (as in case 2 in this report).

A few days later the face was markedly swollen and indurated. Pressure applied to the cheeks caused pitting in the edematous infiltration, indicating that the swelling was largely due to the presence of edematous fluid. On the other hand, the limbs, which at first had shown pitting edema, now disclosed a firm, indurated condition. Several days later the skin of the face became firm and indurated as in "scleroderma," but the integument could still be lifted away from the main

subjacent mass. A roentgenogram of the chest revealed no abnormalities, aside from an increase in the size and density of the hilar shadows and the presence of some calcific deposits. It is interesting that the total protein content was 6.36 mg, with definite inversion of the albumin-globulin ratio (albumin 2.9 mg, globulin 3.46 mg). Subsequently the patient complained of severe pain in the abdomen, and the tissues in this area were found to be diffusely swollen and excruciatingly painful to touch. Throughout this period the temperature was spiking and the pulse rate rapid, about 120 a minute. Some observers felt an enlarged liver, which seemed to indicate a degree of cardiac failure. In order to treat the edematous element in this case, the patient was put on a salt-free diet, and theobromine with sodium salicylate was administered per rectum³⁵. Within several days a remarkable transformation occurred. Large amounts of fluid were voided, the edema of the subcutaneous tissues and muscles diminished, and the patient now appeared markedly emaciated, with muscular wasting apparent. The loss of subcutaneous fat and muscular tissue and the previous edematous stretching of the skin were further emphasized by the rapid appearance of striae atrophicae about the hips, knees, elbows and shoulders. Almost from the onset of the diuretic effect, the patient felt better, he no longer complained of pain in the parts that formerly could not be touched without a reaction of agonizing pains.

On May 16 a sacral decubitus ulcer appeared and was regarded apprehensively. Despite the poor condition of the patient, the defect in the skin closed slowly and spontaneously. The content of urea nitrogen, which on admission had been 40.3 mg, steadily diminished until it reached the level of 18.1 mg. A single determination of the content of calcium in the blood showed it to be 8.8 mg, the phosphorus in the blood was 3.9 mg. The blood pressure was not elevated at any time, an average reading being 126 systolic and 70 diastolic. Examination of urinary specimens continued to show red blood cells, white blood cells and a few hyaline and granular casts. The temperature slowly fell to normal, with occasional interspersed rises. On one occasion a culture of blood revealed an organism in the fluid medium, at first regarded as *Str. viridans*, but later identified as *Str. haemolyticus*. The significance of this finding was somewhat indefinite, but it was decided to administer sulfanilamide. After the intake of the drug, the temperature assumed a normal level and the succeeding cultures of blood were sterile. Nevertheless, the efficacy of sulfanilamide in this case could be questioned, for the bacteriologic findings were of dubious significance, especially in view of the several previous sterile results, the subsequent course was occasionally subfebrile, the tachycardia remained constant, and the patient returned with an exacerbation of the condition. It seems more likely that the results achieved were coincidental, for, aside from an occasional rise in temperature, the patient appeared to be on the road to recovery. After several months of observation, he was sent home, and although there was no fever, the pulse rate hovered about 120 in a minute. Shortly before his discharge from the hospital, the white cell count was 11,000 with 53 per cent polymorphonuclear leukocytes, 43 per cent lymphocytes, 2 per cent eosinophils and 2 per cent monocytes.

Early in the course a piece of skin and muscle was excised for diagnostic purposes. Regarding the pathologic changes and their interpretation, there was some difference in opinion. In addition, the specimen did not contain enough muscular tissue to insure an adequate examination and, moreover, was removed from an area of the body (leg) where the indurative process in the muscles was less conspicuous clinically. The specimen was immediately fixed. It is my

35 Levy, I. J. Personal communication to the author.

purpose to report the observations as interpreted by me and to indicate in what respects others disagreed, so that an unprejudiced account may be given

The material consisted of two separate specimens. One was an elliptic piece of skin and subcutaneous fat, 3.5 by 1.25 by 1 cm. There was no evidence of erythema. On section the tissue was semifirm, and the epithelial layers were not thickened. Another piece of tissue seemed to be muscle, it was a light, grayish-red and presented no other gross pathologic alterations (Dr. A. E. Eisenberg). On microscopic study the following changes appeared significant. The muscle tissue was edematous. Many of the fibers revealed hyaline degeneration, with loss of the transverse striations. In several areas there were accumulations of nuclei that appeared to represent proliferations of sarcolemma nuclei. The blood vessels situated interstitially were sites of a conspicuous infiltration composed chiefly of cells located in the adventitial layer, and apparently these represented an increase in the adventitial cells. Although the blood count had shown an unusual polynucleosis, polymorphonuclear leukocytes were scant. In the interstitial spaces, also, there was evidence of an edematous process.

In the subcutaneous fat there were similar changes in many blood vessels. There was, moreover, in some areas what appeared to be a proliferation of young fat cells, with occasional granulomatous formations. These alterations recalled to my mind the findings in the adipose tissue as recorded by Weber and Gray³⁶ in their report of a case of poikilodermatomyositis.

In the skin proper the changes were chiefly in the deeper layers adjoining the hypoderm. There the bundles of collagen were edematous and stained a pale pink. The vessels showed thickening of the parietes owing to infiltration of fluid and hyaline degeneration, there were occasional collections of nuclei in the subendothelial layer, with narrowing and tendency to closure of the lumens. The vessels were surrounded by periadventitial accumulations of fixed connective tissue cells, a few polymorphonuclear leukocytes and an occasional lymphocyte. Similar, though much milder, changes were observed in the more superficially situated blood vessels in the skin.

There was agreement that the principal pathologic effects had been exerted on the blood vessels in the deeper parts of the skin, subcutaneous tissue and muscle. The chief point of disagreement concerned the interpretation of the observation in the muscle proper. It was, however, conceded that this tissue was edematous and somewhat degenerated (as described in the gross description) and that the wasting observed in this boy was at least partially caused by the loss of muscular parenchyma. It was also agreed generally that the findings were insufficient for the diagnosis of *periarteritis nodosa*.

Addendum—Several months later the patient was again admitted to the hospital during an acute exacerbation of the disease. The outstanding feature at this time was the occurrence of several subcutaneous lumps in the lower limbs giving rise to the clinical impression that the condition was one of *periarteritis nodosa*. Microscopic examination of one of these lesions showed only normal fat and it is possible that the nodule was missed. It is also interesting that on this occasion the musculatures of the upper and lower limbs seemed to approximate a normal state, though their mass was still considerably diminished. It is planned to observe the patient further.

36 Weber, F. P., and Gray, A. M. H. Chronic Relapsing Polydermatomyositis with Predominant Involvement of the Subcutaneous Fat (Panniculitis), *Brit. J. Dermat.* 36: 544, 1924.

COMMENT ON CASE 5

The painful masses of muscle with redness of the overlying integument, the erythematous and edematous swellings about the eyes, the lesions over some of the knuckles and interphalangeal joints and the febrile state, appeared to be consistent with the diagnosis of dermatomyositis. The unusual features were the gross hematuria (sometimes observed in cases of dermatomyositis), the urinary findings, the moderate azotemia and the abnormally high leukocyte count, these anomalies apparently pointing toward periarteritis nodosa. It seemed evident that the chief effects were resident in the blood vessels, though the alterations were not nearly so pronounced as in the "necrotizing arteriolitis" described by Fahr in his report of a case of dermatomyositis. It appears that the primary changes occurred in the vasculature, with secondary effects on the tissues supplied by the affected vessels.

It is interesting that early in the course the muscular swellings in the limbs pitted on pressure and that within a short time the affected areas became indurated and then failed to show pitting. On the face the condition on the latter occasion appeared to be scleroderma, but the skin could still be lifted away in fairly supple folds from the underlying tissue. It is therefore probable that the attribute of firmness was dependent on the degree and type of edematous infiltration occurring in the deeper tissues.

Remarkable was the transformation observed in this patient after the loss of fluid from the tissues, which was brought about by the method stressed by Dr I. Jesse Levy³⁵. Forthwith, the element of pain was relieved, and tissues that at first responded with excruciating pain to touch, now could be handled without pain. The evidence appeared to support the belief of those who thought there was a degree of cardiac failure. In recent years there has arisen a body of opinion that stresses the element of myocardial alterations in occasional instances of dermatomyositis, this aspect of the subject needs further investigation.

The simultaneous involvement of subcutaneous tissue and skin as well as of muscle is a point to stress. The occurrence of striae atrophicae can be attributed to the distention of the superficial tissues by edematous fluid, followed by loss of water, in principle, this is similar to what happens in pregnant women and in persons who have lost weight after a previous state of obesity.

Finally, the persistent tachycardia manifested by this patient is a phenomenon that is often observed in dermatomyositis, its precise genesis is still unknown, though it seems probable that it is bound up in some way with damage to the heart. Such tachycardia may occur in patients with a subfebrile or even normal temperature.

SUMMARY

The protocols of 5 cases are recorded in detail in order to depict the varied manifestations of dermatomyositis as well as to illustrate what may be called a condition "transitional" between that disease and systemic lupus erythematosus. Additional examples of this condition are mentioned only in connection with the elaboration or substantiation of certain points. A preliminary attempt is made to clear the ground for a more detailed consideration of the similarities and the differences in the clinicopathologic features exhibited by each of these diseases in their typical forms.

Two instances of dermatomyositis are described, one very briefly, in which there appeared suggestive evidence that the factor of lead played an important part in the evolution of the clinical picture. These cases are not isolated and are considered in relation to the data indicating that this heavy metal is a vascular poison, especially in certain susceptible persons. These data are carefully reviewed, notably because there is a tendency on the part of observers to attribute various diseases to lead absorption, whenever such views are advanced, critical investigators have, with considerable justification, refused credence to them. Moreover, the cases under my observation did not present the classic evidence of plumbism. Nevertheless, it is suggested that lead may exert a deleterious effect on the blood vessels in especially susceptible persons with a presumably unstable vascular system, and in such persons "vascular disease may be and remain the solitary sign of lead poisoning." The connection between this heavy metal and vascular disease is regarded as probable, even though specific or pathognomonic lesions are not produced. The evidence compiled in this paper cannot be summarily dismissed without further investigation of the problem, which is admittedly difficult.

EFFECTS OF ROENTGEN THERAPY ON HISTOLOGIC PICTURE AND ON SURVIVAL IN CASES OF PRIMARY CARCINOMA OF LUNG

PAUL E STEINER, M D, P H D

CHICAGO

It is the purpose of this paper to present (*a*) a study of the histologic effects of roentgen therapy on primary cancer of the lung, made in an effort to determine the degree of radiosensitivity of this tumor with special reference to its different histologic types, and (*b*) a study of the effects of roentgen therapy on the period of survival in cases of carcinoma of the lung

The idea is prevalent in some places that irradiation is the therapy of choice for primary carcinoma of the lung. Is this view justified? In their accompanying and complementary paper Bloch and Bogardus¹ have presented evidence, based on clinical improvement and on longevity following irradiation, that such treatment is not curative. A search of the literature by them disclosed no authentic cure by irradiation. In postmortem studies I have not observed a primary cancer of the lung to which a lethal dose of roentgen therapy had been given. In fact, the usual experience has been to find that the effect of irradiation, as judged by histologic standards, was far from carcinocidal. It is in an attempt to evaluate the degree of this deficiency that the present study is presented, and it is hoped that by estimation of the effectiveness of technics in use at present the steps necessary to improve therapy will be clarified.

The material on which this study is based consists of 21 patients with primary cancer of the lung who received roentgen therapy and 64 nonirradiated patients used as controls, all of whom have been studied post mortem by members of the department of pathology of the University of Chicago. A study of five irradiated metastatic lesions from carcinoma of the lung is also included. There is a considerable overlap in this series and that studied by Bloch and Bogardus, but the material is not identical, each including many patients not present in the other series. Minor differences consequently appear in the analyses in the two papers, but the general conclusions coincide.

From the Department of Pathology of the University of Chicago

1 Bloch, R G, and Bogardus, G. Bronchogenic Carcinoma, with Special Reference to Results with Roentgen Therapy, Arch Int Med, this issue, p 39

All of the patients, with 2 exceptions, were treated with 200 kilovolts. Most of them were treated with 25 milliamperes, with a few exceptions, in which 5 and 10 milliamperes were used. The half value layer was usually 1.6 mm of copper. The usual focal skin distance was 50 cm, although 5 patients were treated at 80 cm. The primary tumors were usually treated by using three 15 by 15 cm thoracic portals, located anteriorly, laterally and posteriorly. Except in a few instances one portal was treated daily. Further details of treatment are given in the tables and also in each individual case report.

HISTOLOGIC EFFECTS OF IRRADIATION ON CARCINOMA OF THE LUNG

For purposes of analysis the 21 cases have been divided into four groups, according to the tumor dose.

Group 1 (5,000 to 3,020 r)—Five patients received irradiation varying from 5,000 to 3,020 r as calculated for the primary tumor. The

TABLE 1—*Carcinomas Treated with 5,000 to 3,020 Roentgens*

Case	Time of Roentgen Treatments in Days Before Death		Tumor Dose, Roentgens	Histologic Type of Tumor	Histologic Effects
	First	Last			
1	182	121	5,000	Undifferentiated carcinoma	Slight increase in fibrous tissue
2	103	66	4,250	Undifferentiated carcinoma	Necrosis, fibrosis and anaplasia
3	51	27	3,820	Adenocarcinoma	Necrosis, fibrosis and anaplasia
4	169	64	3,450	Undifferentiated carcinoma	Marked necrosis, slight fibrosis and anaplasia
5	152	126	3,020	Squamous cell carcinoma	None

time of the treatment with respect to when the histologic analysis was made, the dosage, the histologic type of tumor and the general results are given in table 1. Other details of the treatment are given in the individual case report. Although 3 of the 5 tumors showed rather marked damage, in no instance was a carcinocidal effect achieved. Two of these 3 tumors showed severe damage, which was lethal to many cells. They were respectively an adenocarcinoma and a completely undifferentiated carcinoma. The third tumor, which showed considerable but less damage, was also an undifferentiated carcinoma. Of this first group of 5 tumors which received large doses, 2 showed no histologic changes attributable to the roentgen treatment. One of these was a highly undifferentiated carcinoma which received 5,000 r. The other was a squamous cell carcinoma which showed considerable keratinization, part of which may, however, have been stimulated by the irradiation.

REPORT OF CASES

CASE 1—This case was one of anaplastic, highly undifferentiated carcinoma (fig 1). Except for a slight increase in fibrous connective tissue no histologic changes could be seen which might be attributed to the irradiation, although it is noteworthy that one hundred and twenty-one days had lapsed since the last treatment was given, and some recurrence of the tumor cells might have taken place to obscure changes previously present. The tumor was composed of small, oval, closely packed cells with very little cytoplasm and dark, dense nuclei. In general

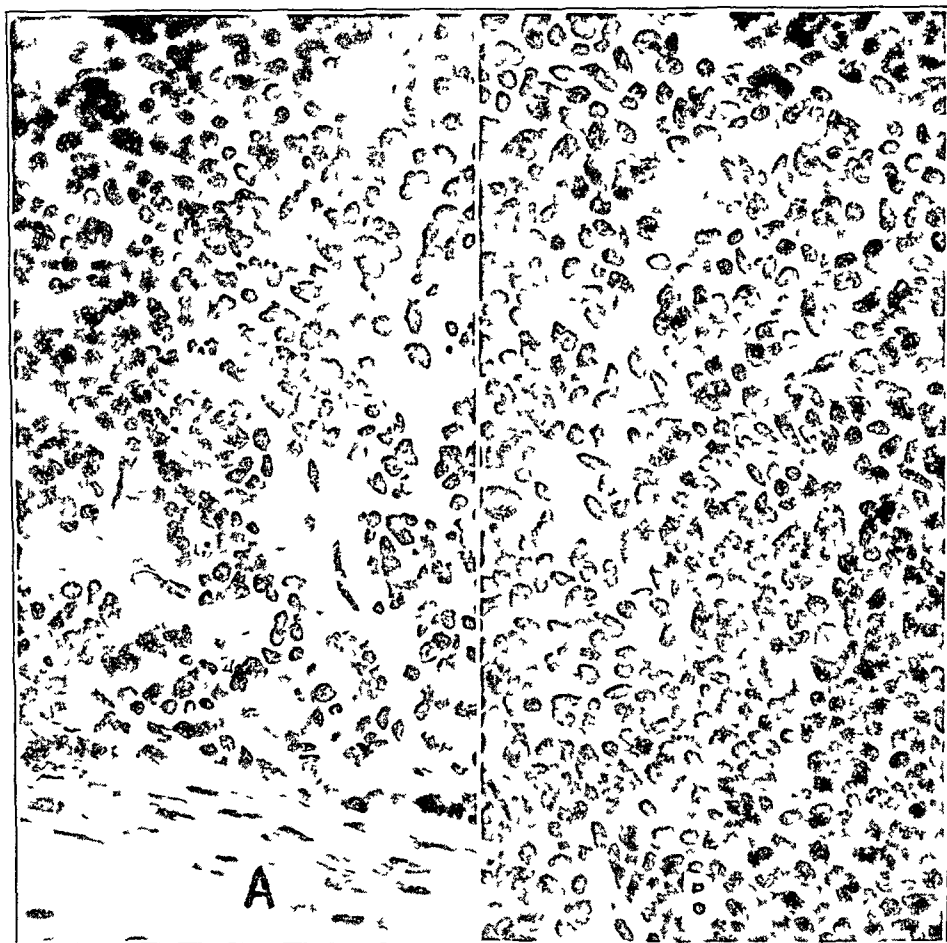


Fig 1 (case 1)—Photomicrographs ($\times 375$) showing the appearance of the irradiated primary lesion in the lung (A) and of a typical nonirradiated metastatic lesion (B). Note the relatively small amount of change produced by 5,000 r.

these cells grew diffusely, but in some metastases, notably the hepatic, they were piled up in thick layers which vaguely resembled transitional epithelium, although the cells themselves did not look like transitional cells. No necrosis was seen at any place in the tumor, and no change had been induced in cell type. Fifteen treatments of 550 r each, the effective dose as measured on the skin, were given in twenty-one days. After a four week rest period fourteen treatments of 550 r each were given in sixteen days.

CASE 2—The cells resembled those in case 1, except that they were slightly larger and showed more variation in size (fig 2). The primary tumor, however, showed moderate changes attributable to roentgen therapy when compared with its metastases. There was marked fibrosis in the primary tumor, but since there was evidence of healed tuberculosis in this region also, the degree of fibrous increase produced from the tumor alone is uncertain. In this fibrous tissue the tumor cells showed marked anaplasia and great variation in size, shape and staining reactions when compared with the distant metastases. While some cells had small pyknotic nuclei, others showed large pale or hyperchromatic nuclei, some

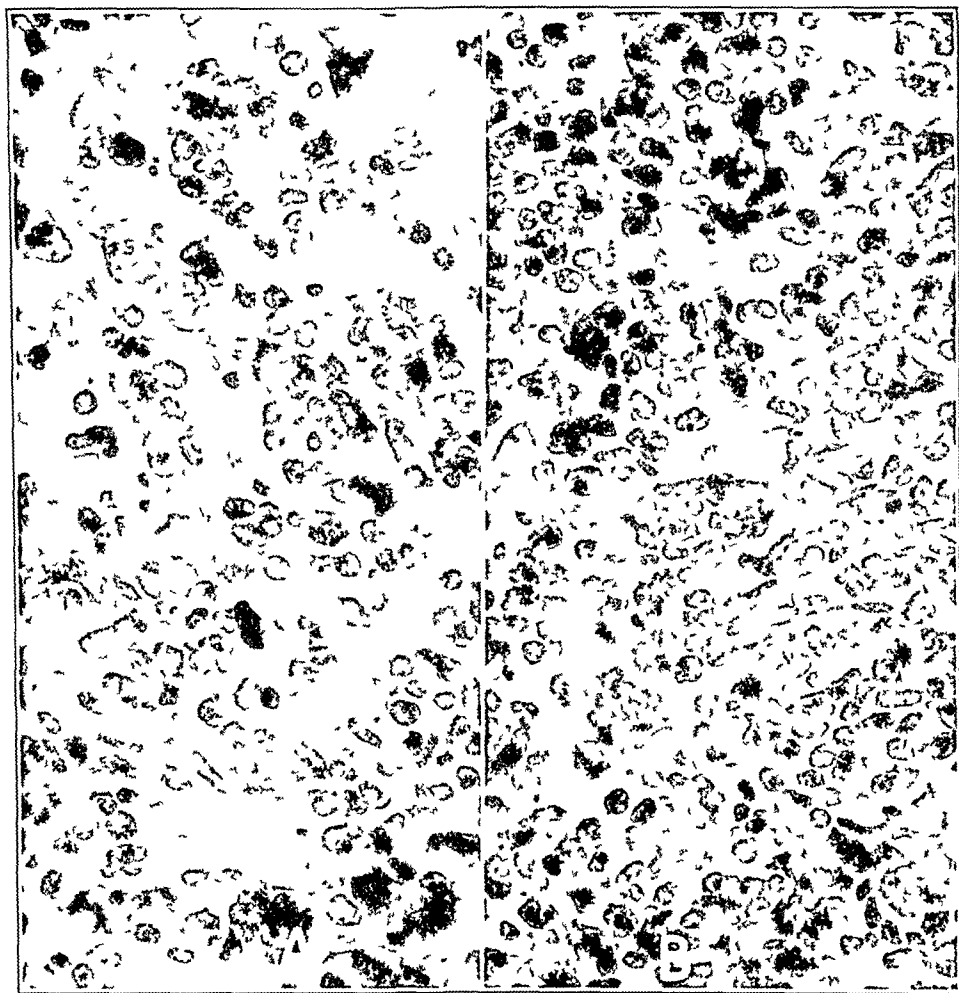


Fig 2 (case 2)—Photomicrographs ($\times 375$) showing the moderate changes induced in a cellularly undifferentiated type of carcinoma of the lung (A) by 4,250 r, with a typical nonirradiated metastatic lesion (B) for comparison

of which were lobulated or even multiple. The cellular cytoplasm was more abundant, and it tended to be more acidophilic. In many places cells had fused to form syncytial masses or giant cells, and in other regions nuclei had degenerated, releasing masses of chromatin dust. Thirty-two treatments of 340 r each, the effective dose as measured on the skin, were given in thirty-seven days.

CASE 3—The tumor was a well differentiated adenocarcinoma with tall columnar mucus-secreting cells which after irradiation showed marked degeneration and disorganization of structure. The arrangement of cells into glands was lost, and the cells were separated and showed marked dedifferentiation or anaplasia,

with numerous giant cells. There were much cell necrosis and lesser degrees of cell damage, consisting of edema and vacuolation of cytoplasm with an increased affinity for acid dyes, with marked pyknosis or karyorrhexis in the nuclei. This case has been previously described in detail by Steiner and Francis,² and additional photomicrographs are shown in figure 3. The patient was given five treatments of 230 r in five days, followed by thirty-four treatments of 310 r, the effective dose as measured in air, in twenty-five days.

CASE 4—The tumor was an undifferentiated carcinoma similar to those in cases 1 and 2. The primary lesion in the lung showed marked retrogressive changes

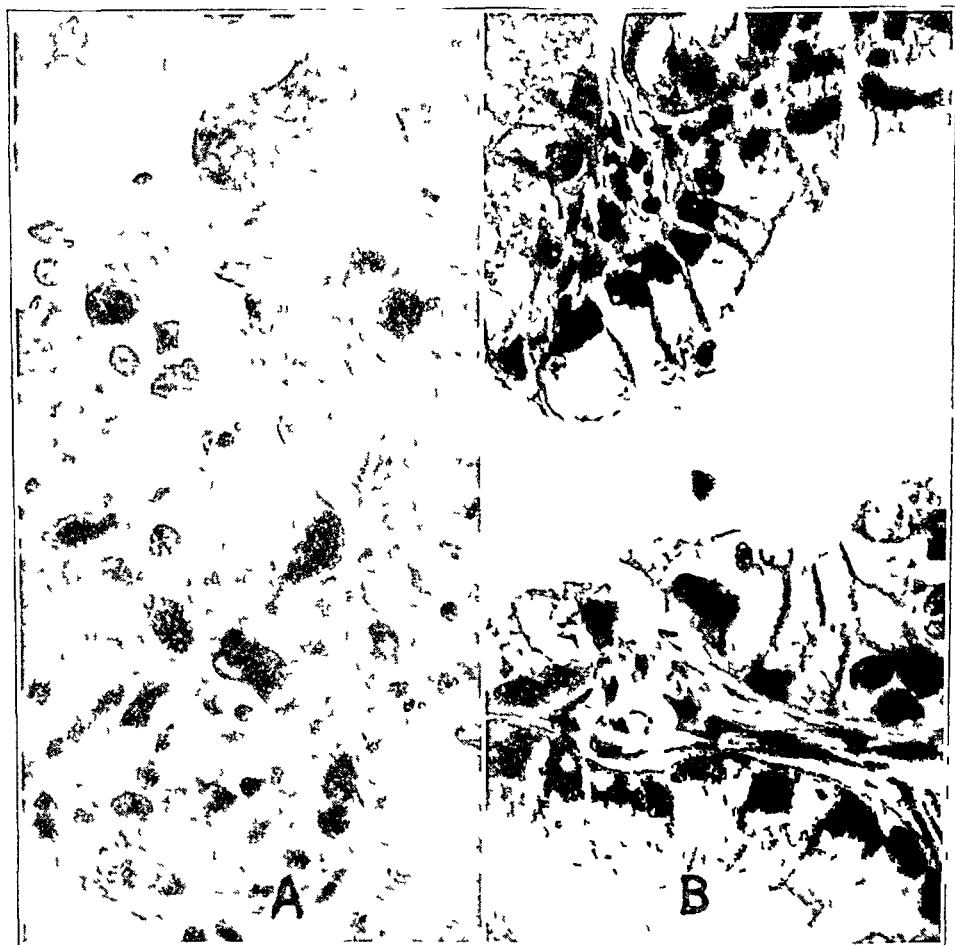


Fig 3 (case 3)—Photomicrographs ($\times 375$) showing the marked changes produced in a primary adenocarcinoma of the lung (A) by 3,820 r and the appearance of a nonirradiated metastatic lesion (B).

attributable to roentgen radiation when compared with the metastases in the non-irradiated liver. There was much active cell degeneration and necrosis, with pyknosis, karyorrhexis and karyolysis, but marked alterations in general cell type were not seen. The patient received 3,600 r in thirty-eight days at another institution, followed by six treatments of 250 r, measured on the skin, in seven days.

2 Steiner, P. E., and Francis, B. F. Primary Apical Lung Carcinoma, *Am J Cancer* 22 776-785 (Dec.) 1934

CASE 5—The tumor was a squamous cell carcinoma which showed no recognizable changes attributable to roentgen radiation. Keratinization may have been induced or hastened, but unfortunately there were no nonirradiated distant metastases available for comparison. Twenty treatments of 325 r, the effective dose as measured on the skin, were given in twenty-six days.

Group 2 (1,890 to 1,035 r)—A tumor dose of 1,890 r to 1,035 r was given in 9 cases, which are summarized in table 2. In this group are 4 examples of squamous cell carcinoma, of which 3 showed marked but sublethal roentgen effects. Two poorly differentiated adenocarcinomas showed no recognizable damage from the irradiation. Two undifferentiated, small-celled carcinomas likewise showed no marked changes. The remaining tumor, a papillary adenoma malignum, also known as bronchial carcinoid or basal cell carcinoma of the bronchus, showed no damage.

TABLE 2—*Carcinomas Treated with 1,890 to 1,035 Roentgens*

Case	Time of Roentgen Treatments in Days Before Death		Tumor Dose, Roentgens	Histologic Type of Tumor	Histologic Effects
	First	Last			
6	1,091	742	1,890	Malignant adenoma	None
7	34	20	1,850	Undifferentiated carcinoma	None
8	232	220	1,740	Squamous cell carcinoma	None
9	9	1	1,670	Squamous cell carcinoma	Acute degeneration, edema and anaplasia
10	14	2	1,490	Squamous cell carcinoma	Necrosis and anaplasia
11	59	22	1,282	Adenocarcinoma	None
12	104	70	1,150	Undifferentiated carcinoma	None, except possibly fibrosis
13	39	29	1,056	Squamous cell carcinoma	Necrosis, fibrosis and anaplasia (roentgen effect?)
14	123	89	1,035	Adenocarcinoma	None

CASE 6—The tumor was an undifferentiated small round to oval cell carcinoma of the papillary adenoma malignum type. Its growth was chiefly intrabronchial but with slight infiltration into the adjacent parenchyma of the lung and metastases only to adjacent peribronchial lymph nodes, in spite of the long duration of the disease. There were no retrogressive changes which could be attributed to irradiation and fewer degenerative changes than would be expected from the age of the tumor. Eleven treatments of 270 r each and eight of 310 r each were given during eight months.

CASE 7—The tumor was a highly undifferentiated and anaplastic carcinoma composed of medium-sized, often polyhedral cells, with a few tumor giant cells, lying in a dense fibrous stroma. There were no visible degenerative changes corresponding to the fairly recent irradiation, and the fibrosis and cellular anaplasia which were present in the pulmonary tumor were equally great in nonirradiated metastases. Ten treatments of 400 r, the effective dose as measured on the skin, were given in fifteen days.

CASE 8—The tumor was a recurrent lesion in the bronchial stump of a squamous cell carcinoma showing keratinization of single cells or of small groups of cells. Although it had been irradiated with 1,740 roentgen units, it did not appear different from a bronchoscopic biopsy section secured prior to irradiation or from sections

made from the tumor which was removed by pneumectomy, also before irradiation. This amount of radiation had not noticeably hastened keratinization or induced anaplasia. It was too long after irradiation to determine whether cell necrosis had been produced, and the differences in the amounts of fibrous tissue are not significant. Twelve treatments of 328 r, the effective dose as measured on the skin, were given in twelve days.

CASE 9—The tumor showed the acute effects of irradiation, therapy having been begun nine days before death and continued until the day before death (fig 4). Elsewhere the tumor was a squamous cell carcinoma with healthy-appearing cells

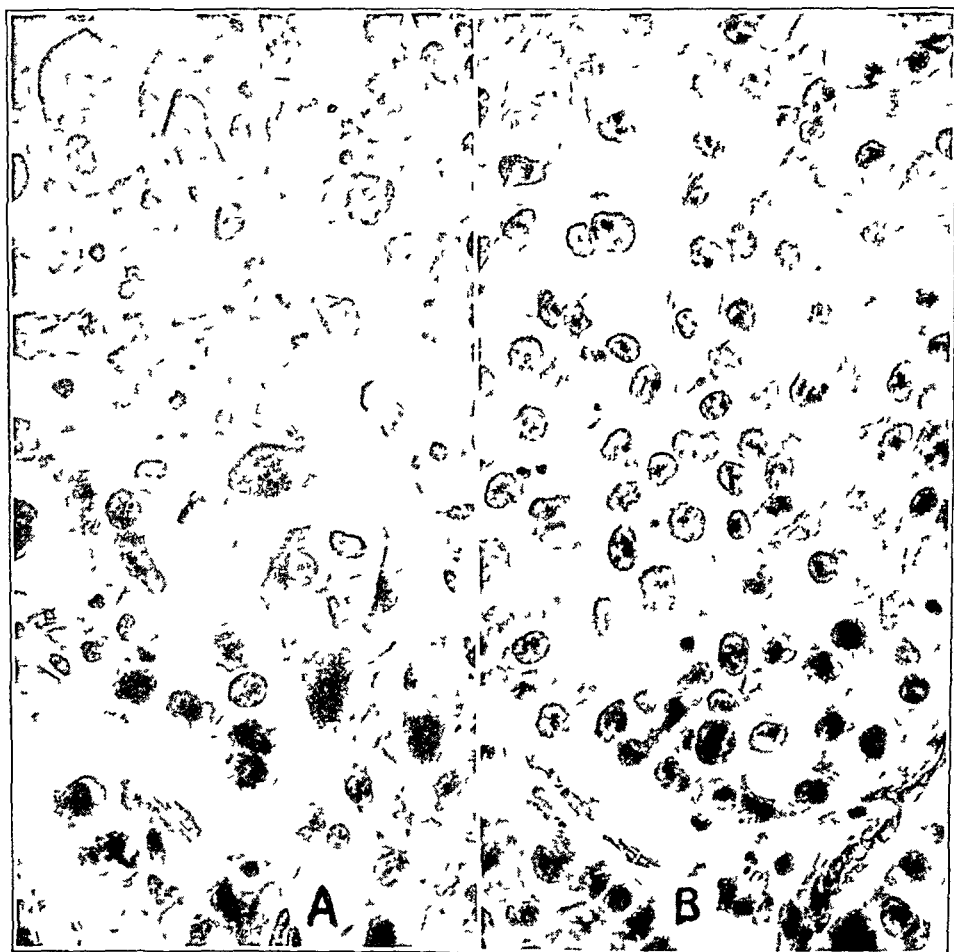


Fig 4 (case 9)—Photomicrographs ($\times 375$) showing the marked changes produced in a primary squamous cell carcinoma of the lung (A) by 1,670 r and the appearance of a nonirradiated metastatic lesion (B).

growing in broad sheets. Keratinization was confined to single cells, and an occasional tumor giant cell was seen. In the irradiated primary tumor, however, edema, anaplasia and acute degenerative changes were seen. The cell masses were distorted or broken up. The cells were separated by intercellular edema and had become rounded. Many giant cells were present. Many cells showed marked vacuolation of their cytoplasm, which in general appeared increased in amount and stained more deeply with eosin. Nuclear changes were also marked and consisted of giant and multiple nuclei, karyorrhexis, some karyolysis and considerable pyknosis. Thirteen treatments of 330 r, the effective dose as measured on the skin, were given in eight days.

CASE 10—This tumor also showed the effects of recent irradiation. Therapy was given from fourteen days to two days before death and was calculated as 1,490 r. The changes consisted of massive necrosis, marked anaplasia and some evidence of hastening of maturation, the irradiated primary tumor being more easily recognizable as a squamous cell carcinoma than were the distant metastases, in which the tumor tissue was more undifferentiated and small celled. The necrosis was massive and was not confined to the poorly nourished centers of cell masses. The cells were separated from each other, were rounded and showed marked variation in size, shape and chromatin content. Bizarre cell forms and giant cells were numerous. In general, the changes resembled those illustrated in case 9, except that necrosis was much greater, edema was less and there was some evidence of hastening of the cell maturation cycle. Nine treatments of 400 r, the effective dose as measured on the skin, were given in twelve days.

CASE 11—The tumor was an undifferentiated adenocarcinoma which showed no changes which could be attributed to irradiation with certainty, although the treatment had been given fairly recently. Retrogressive changes consisting of necrosis and fibrosis were present to approximately equal degrees in the primary tumor and in its metastases. Twelve treatments of 280 r, the effective dose as measured on

TABLE 3—*Carcinomas Treated with 975 to 480 Roentgens*

Case	Time of Roentgen Treatments in Days Before Death		Tumor Dose, Roentgens	Histologic Type of Tumor	Histologic Effects
	First	Last			
15	263	118	975	Adenocarcinoma	None
16	145	119	910	Adenocarcinoma	None
17	135	133	670	Adenocarcinoma	None
18	14	13	480	Undifferentiated carcinoma	None

the skin, were given in fifteen days. After a rest period of three weeks, two treatments (at the same dosage) were given on consecutive days.

CASE 12—The tumor was an undifferentiated, small, oval to round cell carcinoma in which the primary tumor differed from its metastases only in containing more fibrous tissue. There was no alteration in the morphologic character of the tumor cells. Twelve treatments of 275 r, the effective dose as measured in air, were given in thirty-four days.

CASE 13—The tumor was squamous cell carcinoma which showed massive necrosis, marked fibrosis and some cell anaplasia. The role which irradiation played in producing these changes is uncertain, because there were few nonirradiated metastases for comparison. Adjacent to areas showing marked degenerative changes were sheets of fairly healthy-appearing cells. These may, however, have appeared after irradiation. In general the changes resembled those seen in case 10. Eight treatments of 275 r, the effective dose, were given in ten days.

CASE 14—The tumor was an undifferentiated adenocarcinoma in which no changes due to irradiation were visible. Twelve treatments of 350 r, the effective dose as measured on the skin, were given in thirty-five days.

Group 3 (975 to 480 r)—In group 3 are placed 4 cases in which the cancers received between 975 r and 480 r (table 3). There was no evidence of irradiation effect in any tumor in this group.

CASE 15—The tumor was a moderately well differentiated adenocarcinoma which showed no change recognized as due to roentgen therapy. It was moderately

scirrhous in its metastases as well as in the primary lesion, and degenerative changes were approximately equal in all regions. Fourteen treatments of 118 r were given in sixty-seven days.

CASE 16—The tumor, an adenocarcinoma with colloid features, appeared well preserved and approximately identical in all lesions, both primary and metastatic. Nine treatments of 350 r, the effective skin dose, were given in twenty-six days.

CASE 17—The tumor was a well differentiated adenocarcinoma producing much mucin. There was no visible effect of roentgen therapy. Three treatments of 460 r were given on three consecutive days.

CASE 18—The tumor was an undifferentiated carcinoma composed of medium small, dense, compact oval to round cells. It showed no effect of roentgen therapy. Two treatments of 480 r were given in two days.

Group 4 (Unknown Amount)—The pulmonary cancers of 3 other patients were treated by roentgen therapy. The amounts given are not known. In 2 instances the microscopic examination revealed no damage which might be attributed to the roentgen ray. In the remaining case there were degenerative changes, but they were not great, were not definitely due to roentgen damage and were certainly not nearly lethal for the tumor cells.

CASE 19—The primary lesion of the tumor, a large-celled, undifferentiated carcinoma, showed a greater degree of fibrosis and also more recent necrosis than did most of its metastases, except those in the mediastinal lymph nodes. Regardless of whether these changes were induced by roentgen therapy, most of the tumor cells appeared undamaged, and a carcinocidal effect had not been approached. The last treatment had been given twenty-one days before death.

CASE 20—The tumor, an undifferentiated adenocarcinoma, showed no changes suggestive of roentgen damage.

CASE 21—The tumor was an undifferentiated squamous cell carcinoma which showed no damage from the roentgen rays.

HISTOLOGIC EFFECTS OF IRRADIATION ON METASTASES OF CARCINOMA OF THE LUNG

A study has also been made of the histologic effects of roentgen radiation on metastases of carcinoma of the lung in an effort to get further information on its radiosensitivity. Five cases are summarized in table 4. Case 22 is that of a metastasis to the skull in which microscopic examination sixty days after irradiation failed to disclose any living tumor cells. This, therefore, represents the only instance in this entire survey in which a complete carcinocidal effect was observed. It is possible that a more complete microscopic examination might have disclosed some living cells in this instance.

CASE 22—This was the only example encountered in which the cells of a pulmonary carcinoma were killed. The tumor was a cranial metastasis from a primary carcinoma of the lung which was composed of large pleomorphic cells, diffusely growing and undifferentiated. Sixty days after 3,800 r had been delivered to this metastatic lesion it showed no definitely recognizable tumor cells, although a few pyknotic nuclei entrapped in dense collagen may have been forms of surviving

tumor cells Five treatments of 370 r were given in five days After a rest period of one week a second course of the same dose was given After three days of rest five treatments of 245 r were given in five days

CASE 23—The effects of 3,820 r on the primary adenocarcinoma of the lung in this case have been described under case 3 Metastases into the lower cervical vertebral bodies were treated with 2,520 r seventeen days prior to death Microscopic examination of these bony metastases showed them to resemble a metastasis in the ilium which had not been irradiated Whether this failure to produce damage to the carcinoma cells was due to protection by bone or whether it indicates true radioresistance is impossible to say Eight treatments of 415 r were given in nine days

CASE 24—A metastasis in the right ilium, treated with 1,640 r, resembled the primary tumor and numerous other metastases, including some in nonirradiated bones The tumor was an adenocarcinoma Eight treatments of 325 r were given in twelve days

CASE 25—An irradiated metastasis in the brain in this case of carcinoma with pleomorphic, large undifferentiated cells showed a marked degenerative change

TABLE 4—*Effect of Irradiation on Metastases*

Case	Treatment in Days Prior to Autopsy		Tumor Dose, Roentgens	Site of Metastasis	Histologic Type	Effects of Irradiation
	First	Last				
22	80	60	3,800	Skull	Undifferentiated carcinoma	Lethal to tumor
23	26	17	2,520	Vertebral bodies	Adenocarcinoma	None
24	36	24	1,644	Pelvis	Adenocarcinoma	None
25	245	229	1,290	Brain	Undifferentiated carcinoma	None
26	264	239	860	Vertebral body	Adenocarcinoma	None

consisting of massive necrosis and heavy infiltration by polymorphonuclear leukocytes In general, only cells adjacent to blood vessels remained alive This necrosis, however, cannot be entirely, if at all, attributed to the therapy, because much of it was recent, whereas the last irradiation had been given two hundred and twenty-nine days prior to death Twelve treatments of 225 r were given in twenty days

CASE 26—An irradiated metastasis in the tenth dorsal vertebral body showed no effects of the irradiation This lesion was fibrous, but no more so than were nonirradiated metastases Five treatments of 260 r were given in six days

SUMMARY OF HISTOLOGIC CHANGES PRODUCED IN CARCINOMA OF THE LUNG BY ROENTGEN THERAPY

In general, the changes produced by roentgen rays were degenerative in the acute stages and retrogressive in the later stages, accompanied in some cases by profound alterations in cell type None of the individual changes alone are specific for roentgen effects, but taken together at the various intervals the changes are fairly diagnostic Among the 64 nonirradiated controls many instances of degenerative and retrogressive changes were seen which resembled those observed in the irradiated patients, yet the total picture produced by these changes in

any one case was unlike those produced by roentgen rays in individual cases. In evaluating the changes seen in irradiated tumors some reliance was placed on the comparative appearance of their metastases and, in a few instances, on biopsy sections secured prior to therapy.

The most acute changes were seen in cases 9 and 10. They consisted of intracellular and intercellular edema, vacuolation of cytoplasm with an increased affinity for acid dyes and some actual cell necrosis. The nuclear changes at this stage were degenerative and consisted of karyorrhexis, karyolysis or pyknosis. The later stages were those of disorganization of the architecture of the tumor growth and alteration of cell type. As a result of the former, adenocarcinomas lost their ductal or tubular appearance and became more undifferentiated (case 3), and in squamous cell carcinomas the arrangement of cells into squamous epithelium-like layers was lost. Changes in cellular morphologic structure concerned both the cytoplasm and the nucleus. The cells became enlarged, some reaching giant sizes. The cytoplasm stained more deeply with eosin, and it was often granular or vacuolated. The nuclei became more chromatic and were sometimes pyknotic. They tended to be enlarged, and multiple nuclei, ring nuclei, eccentrically placed nuclei and similar phenomena were common. These cellular changes were those of anaplasia or increase in undifferentiation, rather than metaplasia. At this stage there was an increase in fibrous connective tissue in the tumor. This was certainly a relative, and probably an actual, increase.

The number of cases is too small and the factors in therapy are too varied to warrant final conclusions as to the lethal dose and the relative radiosensitivity of the different histologic types of cancer of the lung. However, the evidence presented indicates that the lethal tumor dose would probably be over 5,000 r, although striking effects are produced by smaller doses. The small undifferentiated carcinomas with dark, hyperchromatic nuclei and scanty cytoplasm were less radiosensitive than were the adenocarcinomas and squamous cell carcinomas (tables 1 and 2). This finding was unexpected, because such cells appear more embryonal and undifferentiated, and from knowledge of radiosensitivity of tumor cells in general they would be expected to be more radiosensitive, than are the more highly differentiated types. Nevertheless, the observed fact is that these undifferentiated carcinomas are highly radioresistant.

Perhaps squamous cell carcinoma of the lung can eventually be added to the list of squamous cell carcinomas which are curable by irradiation. This group at present consists principally of carcinoma of the skin, lip, tongue, larynx and cervix of the uterus.

The postmortem histologic examination was made at approximately the time of maximum cellular damage in a few cases, but a glance

at the tables reveals that in others the interval between treatment and examination was so great that much recovery and proliferation of tumor cells had probably occurred. This has been taken into consideration in the text under the individual cases. In the instances in which the interval was great this study does not serve to contribute to knowledge of the radiosensitivity of these tumor cells, but it does give evidence as to their "radiocurability." Effects of radiation on carcinoma of the cervix were studied by serial biopsies by Arneson and Stewart,³ who observed fully active regeneration of carcinoma one to six weeks after the termination of roentgen treatment. It is probable, therefore, that the healthy appearance of the tumor cells in some of the cases presented here is explained by regeneration after the therapy ceased. While this consideration may alter conclusions as to radiosensitivity, it does not affect those made with respect to radiocurability.

Data on the radiosensitivity of carcinoma of the lung comparable to these are scanty in the literature. One of the best studies is that by Herrnheiser,⁴ who stated that the lethal dose is about 9,000 r, measured on the skin. The patient of Jacob⁵ received 8,400 r (measured in air) in twenty-five days for an apical pulmonary tumor of undetermined histologic type, with temporary improvement. Frissell and Knox⁶ stated that in their case XXXVII 5,400 r (measured where?) given during five months caused little improvement of a cuboidal cell tumor. For other references the reader is referred to the monograph by Simons.⁷

EFFECTS OF ROENTGEN THERAPY ON ADJACENT TISSUES AND ORGANS

Observations were made on the condition of tissues and organs which lay near irradiated primary carcinomas of the lung in an effort to detect any possible harmful effect. The adjacent lung tissue, the pleural cavities, the pericardial cavity, the heart, the esophagus and the overlying skin were studied for this purpose. Changes were observed only in the skin, and they were of the types which usually follow such therapy.

3 Arneson, A. N., and Stewart, F. W. Clinical and Histologic Changes Produced in Carcinoma of the Cervix by Different Amounts of Roentgen Radiation. A Comparison, *Arch. Surg.* **31** 542-567 (Oct.) 1935.

4 Herrnheiser, G. Weitere Erfahrungen mit der Röntgenbehandlung maligner Bronchus- und Lungengeschwülste, *Strahlentherapie* **52** 425-459 (March) 1935.

5 Jacob, H. W. Superior Pulmonary Sulcus Tumor, *J. A. M. A.* **103** 84-87 (July 14) 1934.

6 Frissell, L. F., and Knox, L. C. Primary Carcinoma of the Lung, *Am. J. Cancer* **30** 219-288 (June) 1937.

7 Simons, E. J. Primary Carcinoma of the Lung, Chicago, The Year Book Publishers, Inc., 1937.

Adjacent Lung—Although a systematic study of lung tissue through which roentgen rays passed to reach a carcinoma of the lung was not carried out, in the gross descriptions and microscopic sections which are available no important changes definitely due to the therapy were noted. Postmortem material such as this, however, in general is not suitable for accurate studies on this point, because the terminal infections and circulatory disturbances which are so commonly present in carcinomatous lungs complicate and obscure changes which the roentgen treatment may have produced. Pulmonary damage of the types described by Downs,⁸ Schairer and Krombach⁹ and others was not encountered in this study.

Pleural Cavity—The incidence of pleural effusions, focal fibrous pleural adhesions or oblitative fibrous pleuritis on the side of the pulmonary cancer was no greater in the 21 patients who had received roentgen therapy than in the 64 nonirradiated controls. The incidence of such changes was greater on the side of the tumor than on the opposite side in each group.

Pericardial Cavity—The incidence of pericardial effusions and of pericardial adhesions likewise was not greater in the irradiated patients than in those whose tumors had not been irradiated.

Heart—Although fibrous myocardial scars were encountered often in the patients who had received roentgen therapy for pulmonary tumors, the incidence of such focal fibrous myocarditis was no greater than in the nonirradiated patients or in the general postmortem experience with persons of this age group.

Esophagus—No changes were encountered in the esophagus which might have been caused by the roentgen treatment. The incidence of esophageal erosions, peptic esophagitis and leukoplakia of the esophagus was about equal in the irradiated and in the control patients.

EFFECTS OF ROENTGEN THERAPY ON SURVIVAL

The average period of survival after the onset of symptoms in the 53 nonirradiated control patients in whose cases data were available was ten and five-tenths months. The 21 patients treated with roentgen rays survived for an average of eleven and nine-tenths months after the onset of symptoms. This seems to indicate that the irradiation was slightly effective in prolonging life. However, when the following facts are taken into consideration it is clear that the irradiation had no such beneficial action. 1. The series in which irradiation was used included

8 Downs, E. E. Lung Changes Subsequent to Irradiation in Cancer of the Breast, *Am J Roentgenol* **36** 61-64 (July) 1936.

9 Schairer, E., and Krombach, E. Röntgenstrahlenschädigung der Lunge mit tödlichem Ausgang, *Strahlentherapie* **64** 267-290 (Feb.) 1939.

1 case of malignant bronchial adenoma (case 6), a tumor of borderline malignancy and slow growth. In this instance the patient lived for forty-eight months, and even then the tumor was not very large, the patient dying of lobal pneumonia. If this case is excluded, the average duration of survival for the series treated by irradiation was ten and one-tenth months. 2 The control series contained many instances of primary cancer of the lung in which the primary tumor was clinically silent or relatively silent until the last days of life, but in which the clinical picture was dominated by cerebral symptoms due to metastases. In this type of case survival after onset of symptoms is relatively short (four, five, four, four and three months in some of these cases). At this institution such cases are relatively common because of the large neuro-surgical service. Cerebral lesions of this type were not common in the series in which irradiation was used, because in this series the dominant clinical picture of pulmonary neoplasm led to the irradiation therapy. 3 The average period of survival after the first roentgen treatment was given was only one hundred and twelve and seven-tenths days if the case of malignant bronchial adenoma (case 6) is excluded.

It is perhaps unfair to include all of the cases in calculating the influence of irradiation on survival, because in many instances the treatment was given for palliation, with no hope of cure. If one may assume that only when the larger doses were given was an attempt being made to eradicate the tumor, one should properly use only these cases in studying the effects of irradiation on longevity. The patients in cases 1 to 5 (table 1), who received a depth dose of over 3,000 r, had an average survival period of twelve and four-tenths months after the onset of symptoms and one hundred and thirty-one and four-tenths days after the first roentgen treatment was given. The patients in cases 7 to 14 (table 2), who received depth doses between 1,000 and 2,000 r, had an average survival period of nine and five-tenths months from the onset of symptoms and seventy-six and seven-tenths days after the first roentgen treatment. It appears, then, that a vigorous attempt at cure was not particularly effective in prolonging life.

Since this study is based on postmortem material, it is clear that conclusions as to survival and cure following therapy must be made with caution. Cases of complete cure would not be included in a series of this kind. Cures would, however, be detected in a study such as that of Bloch and Bogardus¹. They found none, and their data with respect to longevity correspond closely to those presented here.

There is disagreement in the reports in the literature as to the effectiveness of irradiation in prolonging life. This problem has been reviewed at great length by Simons⁷. Several important factors appear to have been neglected in many of the reported studies. These include failure to recognize the low degree of malignancy of some bronchial

tumors Also, as far as I am aware, no one has studied in a large series of patients the period of survival *after the therapy was given* and compared it with a similar series in which irradiation was not used, calculating in this control series the period of survival from about the same time, namely, when the accurate diagnosis was first made

The question of the palliative effects of irradiation therapy has not been discussed in this paper because the available data were considered inadequate

SUMMARY AND CONCLUSIONS

In 21 cases of primary carcinoma of the lung, irradiation with tumor doses up to 5,000 r did not destroy the carcinoma as judged by histologic standards The smallest dose which produced visible damage was 1,490 r, but the carcinocidal dose is probably above 5,000 r In a metastatic carcinoma of the skull 3,800 r produced marked degenerative changes, apparently destroying the tumor cells although the microscopic examination was not extensive enough to justify a final conclusion Squamous cell carcinomas and adenocarcinomas of the lung were more radiosensitive than were the undifferentiated carcinomas which, contrary to their microscopic appearance, were either highly radioresistant or highly radiorecuperative The histologic changes produced by irradiation consisted of degenerations, retrogressions or alterations in cell type and in tumor architecture, and they resembled those which have been described for other types of carcinoma Undesired effects of irradiation on tissues and organs near the primary carcinomas were not seen Survival was not notably prolonged by irradiation

Most of the radiation therapy was given in the Radiation Clinic of the Division of Roentgenology, which supplied the technical data Dr David Tschetter gave valuable aid in the organization of the material Dr Cornelius Hospers granted permission for use of the postmortem data in case 4

OSCILLOMETRIC READINGS IN CASES OF ARTERIOSCLEROTIC DISEASE OF THE LOWER EXTREMITY

SIGNIFICANCE AND INTERPRETATION

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CLEVELAND

Although oscillometry had previously found widespread use in Europe, it was not until 1927, when Samuels¹ popularized the method, that it began to be extensively used in the United States. Since then, numerous local articles have appeared² discussing the value of oscillometric readings in the study of peripheral arterial disease.

Before my observations concerning the significance and interpretation of oscillometric readings in cases of peripheral arteriosclerosis are presented, some of the well known physical principles on which arterial pulsation is based must be reviewed. When the left ventricle ejects a quantity of blood into the partially filled aorta, pressure changes are suddenly set up in the aorta and in the vessels at the root of the neck. These pressure changes are propagated along the branches of the arterial tree in the form of a wave moving at a speed computed to be eighteen to thirty times as fast as that at which the blood stream moves³. It is this pressure wave which constitutes the pulse, and it is the magnitude of the wave in a segment of an extremity which the oscillometer (with less than 100 per cent accuracy³) measures. As the pulse wave passes

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1 Samuels, S. S. The Value of Oscillometry in the Study of Circulatory Disturbances of the Extremities, *J. A. M. A.* **88** 1780 (June 4) 1927.

2 Silbert, S., and Samuels, S. S. Thromboangitis Obliterans. Prognostic Value of the Oscillometer, *J. A. M. A.* **90** 831 (March 17) 1928. Kramer, D. W. Evaluation of Various Methods of Investigating the Circulation in the Lower Extremities, *Am. J. M. Sc.* **185** 402 (March) 1933. de Takats, G., Hick, F. K., and Coulter, J. S. Intermittent Venous Hyperemia in the Treatment of Peripheral Vascular Disease, *J. A. M. A.* **108** 1951 (June 5) 1937. de Takáts, G. Effect of Sympathectomy on Peripheral Vascular Disease, *Surgery* **2** 46 (July) 1937. Theis, F. V. Popliteal Aneurysms as a Cause of Peripheral Circulatory Disease, with a Special Study of Oscillomographs as an Aid to Diagnosis, *ibid.* **2** 327 (Sept.) 1937. Ochsner, A., and DeBakey, M. The Rational Consideration of Peripheral Vascular Disease, *J. A. M. A.* **112** 230 (Jan 21) 1939. Gardner, C. E. An Instrument to Measure Arterial Pulsation in the Digits, *Surg., Gynec. & Obst.* **69** 103 (July) 1939.

3 Wiggers, C. J. Circulation in Health and Disease, ed. 2, Philadelphia, Lea & Febiger, 1937.

along the arterial tree it gradually becomes "dampened out," so that by the time it reaches the arterioles it has disappeared. As a consequence, there is progressive diminution in the magnitude of arterial pulsation from the proximal to the distal end of an extremity.

There are several reasons for this "dampening out" process, two of the most important being that the arterial tree breaks up into progressively smaller and smaller branches and that, as it does so, a change occurs in the character of the vessel wall. There is a decrease in elastic tissue and a concomitant increase in smooth muscle which are under the influence of a greater or lesser degree of vasoconstrictor tone. By the time the arterioles are reached, there exists for all intents and purposes a system of inelastic tubes, the caliber of which is under the control of nervous, chemical and thermal influences. Without an elastic vessel wall there can be no pulsation. In other words, the existence of arterial pulsation depends on a sudden change in intra-aortic pressure which is propagated to the periphery in the form of a pulsatile wave only because the arterial wall is capable of passive stretching. Thus, arterial pulsation is, in a sense, a by-product of the peculiar structural and functional constitution of the circulatory system, subserving no particular function.

With this preliminary résumé as a background, it is possible to consider the significance and interpretation of oscillometric readings in cases of peripheral arteriosclerosis. First, as to their value in judging the effects of therapy. To give unequivocal information concerning the effects of treatment an instrument must be capable of either directly or indirectly measuring changes in the volume rate of blood flow through the diseased extremity. As has been seen, the oscillometer measures the magnitude of arterial pulsation in a segment of an extremity. The question arises concerning the relation existing between changes in volume rate of blood flow through an extremity and the magnitude of arterial pulsation in it.

Volume rate of blood flow through an extremity is increased chiefly by a decrease in the peripheral resistance brought about by dilatation of the peripheral arteriolar-capillary bed. To accommodate the increased flow of blood there also occurs normally an increase in the caliber of the main arterial trunks. By virtue of this increase in caliber and the concomitant increase in elasticity of the vessel walls through diminution of their tonus, less dampening of the pulse wave occurs, hence there is an increase in the magnitude of pulsation.

However, in the presence of arteriosclerotic disease in which the elasticity of the vessel walls has been impaired, a wide variation in the volume rate of blood flow through the partially occluded vessels occurs without any corresponding change in the caliber or elasticity of the vessels or, consequently, in the magnitude of their pulsation. In addition since a collateral circulation consists of a network of very fine

vessels, the pulse wave may be completely dampened out by the small caliber of these vessels. A patient with complete occlusion of the main arterial trunks may thus have an effective collateral circulation and still present no detectable pulsation. It is for these reasons that oscillometry is of little, if any, value in judging the effects of treatment of peripheral arteriosclerotic disease. I have records of over 50 patients with peripheral arteriosclerotic disease who have obtained definite benefit from various forms of therapy, as evidenced by relief of symptoms and healing of ischemic lesions, without any change in the oscillometric readings.

If oscillometry gives no information concerning the volume rate of blood flow through arteriosclerotic extremities, what is its practical value in the diagnosis of this disease? Since arteriosclerotic disease destroys or impairs the elasticity of the arterial walls, sclerotic arteries either do not pulsate at all or pulsate less than they should, and it was hoped that oscillometry would reveal these decreases in pulsation. Estimation of pulsation in the leg by palpation of the dorsalis pedis and posterior tibial arteries is a crude and inaccurate method. Many patients are seen in whom no pulsation can be detected in either of these arteries, and yet the oscillometer reveals a surprisingly large amount of pulsation in the lower part of the leg. The converse of this is also true, that patients with a degree of arteriosclerotic disease sufficient to produce symptoms may still exhibit palpable pulsation in all the peripheral arteries. It is not sufficiently appreciated that the cold, pulseless foot which blanches on elevation represents a very advanced stage of arteriosclerotic disease. The patient with early involvement may present no objective evidence of the true cause of his symptoms, and it is not unusual to see such a patient treated for a multiplicity of disorders, such as varicose veins, flat feet and rheumatism, until physical findings characteristic of arterial disease make their appearance. It is for this type of patient that a method capable of revealing decreases in arterial pulsation, inferentially due to early arteriosclerotic disease, would be a distinctly valuable diagnostic adjunct. Yet it was with this very type, for which the information was most needed, that the oscillometer proved in my hands to be most disappointing. If the significance of a blood pressure reading is compared with that of an oscillometric reading, the reason becomes apparent. Certain norms have been established for blood pressure readings when a given technic is used, but there is no such thing as a normal oscillometric reading for any given level of an extremity. For example, oscillometric readings taken at the level of the lower part of the leg in persons with normal arteries range between 1 and 10, yet, as will be shown, readings obtained at this level in cases of sclerotic disease often fell somewhere within this range. In other words, an oscillometric reading normal for one person can be grossly subnormal for another.

The problem was to find some simple way of determining whether an oscillometric reading in a case of suspected arteriosclerotic disease of a lower extremity, irrespective of its absolute magnitude, represented a decrease in arterial pulsation. In a recent article⁴ a preliminary report of a new method of applying oscillometry to the diagnosis of arteriosclerotic disease of the lower extremity was presented. Considerable experience with it leads me to believe that it is the answer to the aforementioned difficulties.

Since peripheral arteriosclerotic disease involves the lower extremities to a much greater extent than the upper, it follows that as the disease progresses oscillometric readings taken at any given level in the lower extremities should decrease proportionately more than those at any given level in the upper extremities. To test this hypothesis, a series of oscillometric readings for the lower part of the leg and for the distal third of the corresponding forearm in active young adults free of vascular disease were recorded to establish the ratio that exists normally between oscillometric readings at these two levels. The lower edge of the cuff was placed at the base of the internal malleolus and at the wrist joint. The lower part of the leg was chosen because, with the exception of certain types of pain involving the calf, arteriosclerotic disease of the lower extremity usually manifests itself at or distal to this level. Consequently, information revealing a decrease in arterial pulsation in this segment is particularly significant. In a series of ninety ratios thus obtained, in which the reading at the lower part of the leg was used as the numerator, the lowest ratio was 1. This means that in active adults free of vascular disease the magnitude of arterial pulsation in the lower part of the leg is at least equal to that in the lower part of the forearm.

Therefore, assuming the correctness of the original premise that as peripheral arteriosclerotic disease progresses oscillometric readings taken at any given level in the lower extremities decrease proportionately more than those taken at any given level in the upper extremities, a point should be reached in the course of the disease at which the magnitude of arterial pulsation in the lower part of the leg becomes less than that in the lower part of the forearm and the ratio less than 1. During the past two years this ratio has been computed in every case in which a diagnosis of peripheral arteriosclerotic disease could be made from physical examination. All the patients have been ambulatory. At present over one hundred such determinations have been made, and in every instance the ratio obtained has been less than 1. In approximately 50 per cent the oscillometric reading at the lower part of the leg was 1 or higher despite the fact that in no case could pulsation be palpated.

4 Atlas, L. N. Oscillometry in the Diagnosis of Arteriosclerosis of the Lower Extremities. A New Method of Application, *Arch Int Med* **63** 1158 (June) 1939.

TABLE 1—"Normal" Oscillometric Readings at the Level of the Lower Part of the Leg in the Presence of Arteriosclerotic Disease with Absence of the Pedal Pulses*

Lower Part of Leg	Lower Part of Forearm	Ratio
10	75	0.1
10	50	0.2
15	75	0.2
10	30	0.3
15	50	0.3
20	65	0.3
10	25	0.4
15	35	0.4
35	80	0.4
10	20	0.5
15	30	0.5
25	50	0.5
40	80	0.5
20	35	0.6

* The actual subnormality of these readings is indicated by their ratio to readings taken at the level of the lower part of the forearm

TABLE 2—Instances of Excellent Pulsation at the Level of the Lower Part of the Forearm in the Presence of Advanced Arteriosclerotic Disease of the Lower Extremity

Pulsation in Lower Part of Leg	Pulsation in Lower Part of Forearm	Ratio
0	50	0
0	45	0
0	30	0
Trace	65	0
Trace	40	0
Trace	35	0

TABLE 3—Comparison of Oscillometric Readings for the Lower Part of the Leg with Readings for the Lower Part of the Forearm in Persons with Early Arteriosclerotic Disease of the Lower Extremity*

Age	Symptoms	Palpable Pulse		Oscillometric Readings		
		Dorsalis Pedis Artery	Posterior Tibial Artery	Leg (Lower Part)	Forearm (Lower Part)	Ratio
55	Intermittent claudication, cold foot	Yes	No	10	50	0.2
66	Intermittent claudication, numb foot	Yes	No	10	40	0.25
56	Intermittent claudication frustrans	Yes	Yes	10	40	0.25
53	Intermittent claudication, cold, numb foot	Yes	No	20	40	0.5
68	Cramps in leg, cold, numb foot	Yes	No	40	75	0.5
62	Intermittent claudication, cold foot	Yes	Yes	25	40	0.6
66	Intermittent claudication numb foot	Yes	No	25	40	0.6
55	Intermittent claudication cold foot	Yes	Yes	25	40	0.6
58	Painful, cold, numb foot	Yes	No	25	35	0.7
73	Intermittent claudication, cold, numb foot	Yes	No	30	45	0.7
58	Painful, cold, numb foot	Yes	Yes	35	45	0.7

* Note the characteristic symptoms, the presence of palpable pulsation in the pedal arteries, the oscillometric readings for the level of the lower part of the leg within the "normal" range and the ratios below 1

in the *dorsalis pedis* or the posterior tibial arteries (table 1) Without this method of comparison, such readings would fall within what is considered to be the normal range for oscillometric readings taken at the lower part of the leg Table 2 illustrates the relative freedom of the upper extremity from arterial involvement in the presence of advanced arteriosclerotic disease of the lower extremity

This ratio has been computed also in another group of cases, which in many respects is more interesting In this group, although the symptoms of peripheral arteriosclerotic disease were characteristic, the diagnosis could not be made from physical examination alone Color changes, trophic changes or other objective evidence of diminished circulation were absent In every instance some pulsation could be detected in the *dorsalis pedis* artery, and in some instances there was pulsation in the posterior tibial artery as well These cases represent as early a stage of peripheral arteriosclerotic disease as one sees clinically (table 3)

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RELATION BETWEEN MULTIPLE PERIPHERAL NEUROPATHY AND CIRRHOSIS OF THE LIVER

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Rolleston and McNee,¹ in their splendid book on diseases of the liver, gallbladder and bile ducts, stated

The minor degrees of peripheral neuritis are often thrown into the shade by ascites or other effects of cirrhosis on which attention is focused, and so pass undetected Cramps, muscular tenderness and loss of the tendo Achilles and knee jerks may occur in cases of cirrhosis admitted for ascites or hematemesis, and are, generally speaking, to be referred to alcoholism Peripheral neuritis in the early stages of cirrhosis is usually alcoholic, it may be due to a combination in varying degrees of alcoholism and hepatic insufficiency

It is the purpose of this paper to examine the connection between peripheral neuropathy (to use the term proposed by Wechsler² to replace peripheral neuritis) and hepatic cirrhosis in the light of the evidence which has recently been given on the etiology of the former condition and to present our own statistics on the subject

A moving account of the rapid development of coexisting peripheral neuropathy and cirrhosis of the liver in a 30 year old alcoholic woman was reported by Lancereaux³ in 1865 In 1896 Gouget⁴ reported the case of a woman who was admitted to the hospital for cirrhosis of the liver On entry she stated that she had cramps in the calves Within two months she had severe neuropathy involving the motor and sensory portions of the nerves of both extremities The neuropathy was proved at autopsy two weeks later According to Gouget, the source of the

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1 Rolleston, H, and McNee, J W Diseases of the Liver, Gallbladder and Bile Ducts, ed 3, New York, The Macmillan Company, 1929, p 314

2 Wechsler, I S Multiple Peripheral Neuropathy Versus Multiple Neuritis, J A M A **110** 1910-1913 (June 4) 1938

3 Lancereaux, E Studies on Alterations Produced by the Abuse of Alcoholic Beverage, Gaz hebdomadaire de medecine et de chirurgie **2** 435-439 (July 14) 1865

4 Gouget, A Hepatic Insufficiency and Peripheral Neuritis, Revue de medecine **17** 537-546 (July) 1897

nerve lesion was hepatic insufficiency By 1904 Santon and Castaigne⁵ had collected 7 other cases, including 2 of their own In 1907 Guillaumot⁶ was able to find 18 cases

In 1908 Klippel and Lhermitte⁷ summarized the French literature up to that time in an excellent article in which they reported 3 personal cases and analyzed the problem from the clinical, pathologic and etiologic points of view They recognized two types of neuropathy, one appearing as a terminal phenomenon in moribund persons with cirrhosis, the other occurring distinctly earlier in the disease The former they associated with cachexia and malnutrition and considered a degenerative process associated with toxic products of cachexia They stated that alcohol need not be connected with this type of neuropathy The more common type of polyneuritis they found in conjunction with a large liver and marked alcoholism, usually in women between the ages of 30 and 40 They concluded that this type of neuritis (which they labeled definitely inflammatory) is not essentially different from that occurring in persons with alcoholic polyneuritis uncomplicated by cirrhosis The fact that the polyneuritis was often severe was attributed to the circumstance that the hepatic disease lowered the antitoxic function of the liver, so that the noxious properties of alcohol (or of some substance contained in the spirits consumed) were not neutralized and could work freely on the tissues of the nervous system

Rolleston and Fenton⁸ reported the necropsy observations in 114 cases of cirrhosis in 1896 In 3 cases (in all of which the patients were females) death was considered due to the alcoholic neuritis which developed late in the course of the disease Candler⁹ found 4 of 82 deaths due to neuritis

A few years later Eppinger and Arnstein¹⁰ remarked that polyneuritis probably occurs more often in connection with disease of the liver than one would suspect from the literature They reported 6 cases of neuritis, in 2 of which the patients were obviously cirrhotic (1 a nonalcoholic patient) The other 4 had disturbances of hepatic physiology as judged by tests of hepatic function, 2 of these had large livers

5 Santon, P, and Castaigne, J Coexistence of Alcoholic Cirrhosis and Peripheral Neuritis, *Arch gen de med* 2 2446-2455, 1904

6 Guillaumot, H L, cited by Klippel and Lhermitte⁷

7 Klippel, M, and Lhermitte, J Neuritis in the Course of Cirrhosis of the Liver, *Semane med* 28 13-17 (Jan 8) 1908

8 Rolleston, H, and Fenton, W J On the Cirrhotic Liver, *Birmingham M Rev* 40 193-215, 1896

9 Candler, J P A Comparative Inquiry into the Incidence of Cirrhosis of the Liver at Charing Cross Hospital and Claybury Asylums, *Arch Neurol*, Claybury 3 441-446, 1907

10 Eppinger, H, and Arnstein, A On the Pathogenesis of Polyneuritis, *Ztschr f klin Med* 74 324-333, 1912

In all cases the nerve involvement was severe and was the reason for hospitalization

In more recent years the subject of neuropathy in connection with cirrhosis has been comparatively neglected. In his textbook on diseases of the liver, published in 1935, Weiss¹¹ mentioned only that "cirrhotic patients are frequently attacked by neuritis particularly when alcoholic paralysis is located in the lower extremities." In his authoritative book published in 1937, Eppinger¹² stated that polyneuritis occurs in 3 per cent of persons with cirrhosis. Individual cases have been reported by Barker¹³ and by Meyers¹⁴.

Mancke¹⁵ considered peripheral nerve changes rare in cirrhosis than in metabolic diseases, such as diabetes. He reported 5 cases in which there was isolated absence of the knee and ankle jerks, 1 of these was a case of pigmentary cirrhosis (previously reported by Nakano¹⁶), 1 was a case of cirrhosis associated with diabetes and 3 were cases of pigmentary cirrhosis with diabetes.

With regard to etiology, Rolleston and McNee¹ summed up general opinion in 1929:

The terminal stages of cirrhosis are marked by symptoms due to hepatic insufficiency, such as epistaxis and other hemorrhages, delirium and coma. The toxic coefficient of the urine will, if the kidneys be healthy, become increased as a result of the liver failing in its antitoxic function, and a toxemic neuritis may result. If alcohol has been taken recently, the neuritis must be considered to be due to this cause, but in the absence of this factor hepatic insufficiency with resulting toxemia is a satisfactory explanation. Very little alcohol may cause neuritis in advanced cirrhosis.

These views combine those of Klippel and Lhermitte⁷ and those of Gouget,⁴ expressed many years before.

Eppinger and Arnstein¹⁰ concluded that a toxin retained in the liver or one unchanged by the intestine might be responsible for the development of neuritis or that the hepatic insufficiency and polyneuritis might both be the result of a third factor. They suggested that this hypothetical factor might be a fluorescent substance, such as hematoporphyrin.

The conception of peripheral neuropathy as the result of vitamin B deficiency has now been established on a sound footing. The role of

11 Weiss, S. Diseases of the Liver, Gall Bladder, Ducts and Pancreas Their Diagnosis and Treatment, New York, Paul B. Hoeber, Inc., 1935, p. 412.

12 Eppinger, H. Die Leberkrankheiten, Berlin, Julius Springer, 1937.

13 Barker, L. F. Chronic Alcoholism with Cirrhosis, Hepatitis, Polyneuritis and Personality Disorder, Internat. Clin. **1** 17-35 (March) 1929.

14 Meyers, F. M. Conditioned Deficiency Especially in Cirrhosis of the Liver, Geneesk. tijdschr. v. Nederl.-Indië **77** 1155-1162, 1937.

15 Mancke, R. Peripheral Neuritis in Pigmentary Cirrhosis, Deutsche Ztschr. f. Nervenhe. **125** 279-285, 1932.

16 Nakano, J. Hemachromatosis Resembling Addison's Disease, München med. Wchnschr. **61** 919-923 (April 28) 1914.

alcohol as a direct toxic agent was ruled out by Strauss¹⁷ and by Blankenhorn and Spies¹⁸ Jolliffe and his collaborators¹⁹ have successfully treated a large number of patients with peripheral neuropathy with crystalline vitamin B₁ and with concentrates of the vitamin B complex

Goodhart and Jolliffe^{19a} included several cases of cirrhosis of the liver in their study on the effects of vitamin B therapy on the polyneuritis of alcoholic addicts They obtained improvement in the neuropathy and also in the general condition of the patient

The following series represents a summary of cases in which the patients were admitted to the Stanford Medical Service of the San Francisco County Hospital and discharged with a diagnosis of cirrhosis of the liver The records reviewed cover the period from July 1, 1928, to Jan 1, 1939 There are included a total of 272 patients, with 317 entries Readmissions for abdominal paracenteses and most other causes were excluded However, readmissions because of a flare-up in the hepatic process were considered fairly within the province of this thesis and were included The intervals between admissions in these cases varied from a few months to eight years There was liable to be a diagnosis of neuritis on one admission and not on another As may be seen (table 2), the percentage of readmissions among the patients with neuropathy was nearly the same as among those without it In most of the cases the diagnosis of peripheral neuropathy was not the primary one

Care was taken to eliminate so-called fatty alcoholic livers with peripheral neuropathy The criteria used were (1) the pathologist's diagnosis in case of death, (2) laboratory tests, including the retention of bromsulphalein dye, the Takata reaction and the degree of anemia, (3) the history, (4) the physical signs, including the development of ascites, the collateral circulation and the presence or absence of gastrointestinal hemorrhage, and (5) the course under subsequent observation Use was made of these same criteria in an attempt to grade cirrhosis in three stages—early, moderately advanced and far advanced

The criteria used for the diagnosis of peripheral neuropathy were a history of pain, burning, numbness or weakness in the limbs, paresthesia, tenderness of the calves, paresis, paralysis and atrophy of muscles and

17 Strauss, M B The Etiology of "Alcoholic" Polyneuritis, *Am J M Sc* **189** 378-382 (March) 1935

18 Blankenhorn, M A, and Spies, T D Prevention, Treatment and Possible Nature of the Peripheral Neuritis Associated with Pellagra and Chronic Alcoholism, *Tr A Am Physicians* **50** 164-166, 1935

19 (a) Goodhart, R, and Jolliffe, N Effects of Vitamin B (B₁) Therapy on the Polyneuritis of Alcohol Addicts, *J A M A* **110** 414-418 (Feb 5) 1938
(b) Jolliffe, N, and Colbert, C N The Etiology of Polyneuritis in the Alcohol Addict, *ibid* **107** 642-647 (Aug 29) 1936

alterations of the patellar and ankle tendon reflexes. No one sign alone was taken as diagnostic. In the majority of the cases there was no more than tenderness of the calves, absent ankle jerks, edema of the dorsa of the feet and wasting of muscles. It is to be emphasized that this series includes a large percentage of cases of mild multiple peripheral neuropathy as well as a few cases of severe involvement of the type which most previous authors have reported.

The following case is presented as an illustration.

REPORT OF A CASE

E. J., a woman aged 44, was admitted to the hospital Feb. 4, 1938. She had first been admitted to the San Francisco Hospital in 1930, complaining of nausea, vomiting and anorexia. Her condition was then diagnosed as cirrhosis of the liver, chronic alcoholism and syphilis. At that time there was no jaundice or enlargement of the abdomen. She had mild peripheral neuropathy and tenderness of the liver. Her second entry was in 1933, for alcoholism and a flare-up of hepatitis. There was no icterus. No spider hemangiomas were present, and there was no peripheral neuropathy. The liver was palpable 15 cm. below the right costal margin, it was slightly tender and not hard. The complaints were again of nausea and vomiting. No ascites was recorded. Mild anemia was present on both entries.

On her third entry (the present) there had been six months of progressive weakness, epigastric discomfort, attacks of nausea and gagging. Recently she had been unable to walk. Soreness of the legs, numbness of the hands and enlargement of the abdomen had developed.

Physical Examination—The patient was dull, apathetic and stupid appearing, with wasted muscles and a large, fluid-containing abdomen. Spider hemangiomas were present. There was no icterus. The liver was palpable 4 cm. below the right costal margin and was hard and tender. The teeth were in bad condition. There was tenderness over the calves and marked weakness of the hands and legs. The tendon reflexes were absent.

Laboratory Data—The value for hemoglobin was 70 per cent. There were 3,470,000 red cells and 14,400 white cells per cubic millimeter of blood. There were 74 per cent neutrophils. The sedimentation rate was 42 mm. in one hour. The mean corpuscular volume was 109. The Takata reaction was 00110000 in the blood and 01100000 in the ascitic fluid. The value for serum protein was 68, globulin 42. The icterus index was 9. The value for blood urea was 22 mg. per hundred cubic centimeters. There was no urobilin or bile in the urine. The Wasserman reaction was negative. The protein content of the spinal fluid was 50. The Pandy test showed a faint trace of globulin. The Wassermann reaction was negative. The Lange curve was 1111221100.

Course—The patient was kept one month in the hospital under the routine ward regimen, without change except that she became unable to walk. Beginning on March 7, she was placed on a high vitamin, high carbohydrate, low fat diet and given 66 mg. of thiamine chloride daily. From this time on she showed gradual but steady improvement. After four weeks she was much more wide awake and mentally clear, had a fairly decent appetite, was beginning to gain weight and had softer skin. She still showed numbness of the hands. The dose was raised to 132 mg. daily on April 4. The improvement in her condition was

accelerated She was discharged on April 22 "feeling better than she had in years" The appetite was excellent, the skin was velvety There was no evidence of ascites The liver was down 5 cm There was no tenderness in the calves Strength was improved in both hands She was walking freely and helping make beds The value for hemoglobin was 82 per cent There were 4,030,000 red blood cells per cubic millimeter The mean corpuscular volume was 96.7 The Takata reaction was 00000000

Summary—This was a case of moderately advanced cirrhosis of the liver and multiple peripheral neuropathy with at least three flare-ups of hepatitis Improvement followed administration of a high vitamin, high carbohydrate diet and of

TABLE 1—*Summary of All Admissions for Cirrhosis of the Liver from July 1928 to January 1939*

	Number	Per Cent
Entries	317	
Cases	272	
Sex		
Males	183	58
Females	134	42
Stage		
Advanced	168	53
Moderate	87	27
Early	62	20
Mortality		
Per entry	149	47
Per case	149	55
Signs		
Neuropathy	55	17
Large liver	235	74
Ascites	203	64
Jaundice	182	58
Gastrointestinal hemorrhage	110	35
Weakness	179	56
Associated conditions		
Pellagra	10	3
Deficient diet	72	23
Alcoholism	230	72
Laboratory data		
Takata reaction obtained	148	47
Positive Takata reaction	110	74
Hemoglobin estimated	296	93
Hemoglobin under 70% (Sahli)	143	48

thiamine chloride The rate of improvement accelerated when the dose was doubled During the course of treatment the macrocytic anemia diminished and precipitation in the Takata reaction disappeared

COMMENT

In table 1 are summarized a number of facts which indicate the condition of the patient with regard to various aspects of cirrhosis other than peripheral neuropathy males were more common than females, in a ratio of about 6 to 4 In four fifths of the patients the condition was regarded as far advanced or moderately advanced

With regard to specific diagnostic symptoms and signs, one third of the patients had had hemorrhage from the gastrointestinal tract, over one half had weakness as an outstanding complaint Six of 10 had a lesser or greater degree of jaundice (jaundice in these patients means either distinct clinical jaundice or an icterus index of 12 or more)

The liver was considered large in three fourths. Anemia, as gaged by a hemoglobin content of below 70 per cent (Sahli), was found in one half. The Takata test was performed as a routine procedure on over one half. In 74 per cent the reaction was positive—a lower percentage of positive Takata reactions in cases of cirrhosis of the liver than was found by us previously but fitting in with general experience when the test has been done routinely.²⁰

TABLE 2—*Analysis and Comparison of Data on Entries for Cirrhosis With and Without Peripheral Neuropathy from July 1928 to January 1939*

	Cirrhosis with Peripheral Neuropathy		Cirrhosis Without Peripheral Neuropathy	
	Number	Per Cent	Number	Per Cent
Entries	55		262	
Cases	48	87	224	85
Sex				
Males	20	36	163	62
Females	35	64	99	38
Stage				
Advanced	24	44	144	55
Moderate	14	25	73	28
Early	17	31	45	17
Mortality				
Per entry	24	44	125	48
Per case	24	50	125	56
Signs				
Large liver	47	86	188	72
Ascites	31	56	172	66
Jaundice	31	56	151	58
Gastrointestinal hemorrhage	17	31	93	36
Weakness	38	69	141	54
Associated conditions				
Alcoholism	50	91	180	69
Deficient diet	22	40	51	20
Pellagra	4	7	6	2
Laboratory data				
Positive Takata reaction	26	72	84	75
Hemoglobin under 70% (Sahli)	23	50	120	48

A history of alcoholism was noted in more than 70 per cent of cases. Pellagra was present in 3 per cent. A deficient diet was admitted in 23 per cent. The mortality by entry was 47 per cent. The mortality by case was 54 per cent.

Peripheral neuropathy was diagnosed in 55 of the 317 entries, or 17 per cent (table 2). If the figures in the cases in which peripheral neuropathy was present are compared with those in which it was not diagnosed, certain differences are found. In the group of patients with neuropathy there was a reversal of the sex ratio, 64 per cent being female as opposed to 38 per cent of the remaining patients. The per-

²⁰ Wayburn, E., and Cherry, C. B. The Takata Reaction in the Blood Serum, *Am J Digest Dis* 5: 231-238 (June) 1938.

centage of cases in which the cirrhosis was graded as "early" was greater in the group with neuropathy, being 31 per cent as opposed to 17 per cent in those without nerve involvement. In line with this was a lower incidence of gastrointestinal hemorrhage and ascites. The occurrence of a large liver was slightly more frequent. The complaint of weakness was more obvious (69 per cent as compared to 54 per cent). The mortality rate was lower. The average age was several years less for the patients with neuropathy. The incidence of alcoholism, of admitted dietary deficiency and of pellagra was markedly increased in this group. Ninety-one per cent of the patients with neuropathy admitted alcoholism, as opposed to 69 per cent of those without neuropathy. Forty per cent

TABLE 3—*Increased Incidence of Cirrhosis of the Liver with Peripheral Neuropathy (July 1928 to January 1939)*

Year	Total Admissions*	Total Entries for Cirrhosis, Number	Entries for Cirrhosis and Peripheral Neuropathy	
			Number	Per Cent
1928 (6 mo.)	548	8	0	0
1929	1,098	13	0	0
1930	1,223	16	2	12
1931	1,294	13	0	0
1932	1,262	21	2	10
1933	1,289	31	4	13
1934	1,177	27	1	4
1935	1,158	32	5	16
1936	1,357	61	13	21
1937	1,406	46	6	13
1938	1,357	49	22	45
Total	13,169	317	55	17

* All figures refer to admissions to the general medical service (Stanford University) of the San Francisco Hospital. The only figures available for total admissions are scheduled on the fiscal year (July to July). To reach the figures listed, the total for each fiscal year has been halved and the resulting half combined with the total for half the succeeding year.

with nerve lesions admitted having taken an inadequate diet, while a similar history was obtained in only 20 per cent of the remaining cases. Finally, 7 per cent of the cirrhotic patients with multiple neuropathy had associated pellagra, whereas only 2 per cent of those without the former deficiency disease had the latter one.

If the figures are broken down and the entries recorded by years (table 3), two important statistical facts become apparent. First, there has been a marked increase in the number of patients with cirrhosis of the liver admitted to the San Francisco Hospital since 1933, which has been even more accentuated since 1936. Second, there seems to have been a tremendous rise in the incidence of coexisting multiple peripheral neuropathy and cirrhosis. However, the latter change coincides with the appearance of a personal interest in this problem, with the result that patients with cirrhosis have been more carefully investigated. Prior to this only a high grade of neuropathy was thought worthy of note.

If the neuropathy was mild, if the patient had been recently drinking or if the neurologic signs cleared during the stay in the hospital, the neuropathy was liable to be overlooked. The recorded incidence of over 45 per cent of the 49 cases of cirrhosis observed in 1938 is considered by us much closer to the true situation than the 7 per cent recorded in 129 admissions for the years 1928 to 1934.

Evaluation of Therapy—An attempt has been made to evaluate the therapy of patients having cirrhosis with multiple peripheral neuropathy. High vitamin diets, liver extract²¹ and various preparations of vitamin B were used. Vitamin B concentrates (brewer's yeast and wheat germ extract) were given in doses ranging from 1,000 to 4,000 international units (of thiamine) daily. Thiamine chloride²¹ was administered orally or parenterally in amounts varying from 5 to 60 mg daily. Treatment was usually begun after a control period and continued throughout the stay in the hospital.

In 24 of the cases of cirrhosis complicated by peripheral neuropathy the patients were in the terminal stage of cirrhosis. Large doses of thiamine chloride (up to 60 mg daily) were given parenterally to 4 of these patients without any demonstrable effect on either the cirrhosis or the neuropathy.

Among the 31 who survived, 6 were treated with high vitamin diets and liver extract. Ten others received, in addition, vitamin B concentrates with or without thiamine chloride. Four of the 6 patients receiving the former, and all of the 10 patients receiving the latter treatment showed clearing of their subjective and objective neurologic symptoms during their residence in the hospital (a matter of a few weeks in most instances).

Clearing of neurologic signs also occurred in a certain number of patients who received no therapy other than the regular hospital diet (which has a vitamin content above the average). Of 15 such patients in this series, 9 showed eventual improvement. The regression of signs seemed to occur more rapidly in the adequately treated patients. In only a few was it dramatic.

COMMENT

The occurrence of multiple peripheral neuropathy in such a high percentage of cases of cirrhosis of the liver seems a fact of importance. The increase in the amount of hepatic cirrhosis itself seen at this hospital in the past few years is marked. This, as well as the apparent startling rise in the percentage of cirrhotic persons who have the complication of peripheral neuropathy, is probably related to the increase in admissions of patients with alcoholism to the hospital. Another factor in the

²¹ Eli Lilly & Co. supplied generous amounts of thiamine chloride (betalm S) and liver extract.

apparent increase in neuropathy, as has been pointed out earlier, is awareness of the problem

Early cirrhosis was seen more often in the group of patients having peripheral neuropathy, for several reasons. The neuropathy itself may have been the patient's chief complaint. It may have imposed an additional set of symptoms, i. e., just enough more to make the patient seek medical aid. Or it may have been associated with another syndrome, such as some other deficiency disease, acute alcoholism or postalcoholic gastritis.

The observation that cirrhosis accompanied by peripheral neuropathy is more common in females whereas cirrhosis alone is found predominantly in males is an interesting although as yet unexplained observation which has been noted by others¹ as well as ourselves.

The connection between peripheral neuropathy and cirrhosis may help in throwing light on the etiology of the latter condition. There are associated, in too high a percentage incidence to be coincidental, two diseases, one with and one without known etiologic factors. If peripheral neuropathy may be regarded as a fairly reliable sign of deficiency of vitamin B₁, the obvious inference is that there is in cases of cirrhosis a deficiency of thiamine. It does not follow that thiamine deficiency is the cause of hepatitis or that thiamine protects the liver from injury. We are at present investigating the effect of thiamine in cases of experimental damage to the liver.²²

It is becoming increasingly apparent that vitamin deficiencies rarely occur singly. This may be said particularly of the various members of the so-called vitamin B complex. Although the increased incidence of pellagra is the only aspect of such deficiency offered statistically in this paper, we have not infrequently observed other types of deficiency disease in patients with cirrhosis of the liver. Jolliffe,^{19a} Patek²³ and we have observed clinical improvement in the general well-being of cirrhotic patients at the same time that their neuropathy regressed under treatment with large doses of vitamin B. It is possible that the vitamin B complex may contain a liver-protective factor. Gyorgy and Goldblatt²⁴ kept a colony of rats on a diet deficient in the vitamin B complex and supplemented by vitamin B₁ and B₆ and riboflavin. In 48 of these they observed changes in the liver, ranging from parenchymatous and fatty degeneration to cirrhosis. These changes could be prevented by the addition of yeast to the diet.

22 Wayburn, E., and Cox, A. J. Unpublished data.

23 Patek, A. J., Jr. Treatment of Alcoholic Cirrhosis of the Liver with High Vitamin Therapy, *Proc Soc Exper Biol & Med* **37** 329-330, 1937.

24 Gyorgy, P., and Goldblatt, H. Hepatic Injury on a Nutritional Basis in Rats, *J Exper Med* **70** 185-192 (Aug) 1939.

Rich and Hamilton²⁵ fed rabbits diets supplemented by various vitamins. Cirrhosis of the liver occurred in all of 14 rabbits the diets which lacked yeast. This cirrhosis resembled Laennec's cirrhosis in man. It was not prevented by the specific addition of vitamins B₁, G(B₂), and B₆, and nicotine acid to the diet but was prevented by the addition of brewer's yeast.

Wilbur and Snell²⁶ have summarized the role of the gastrointestinal tract in the development of deficiency states as (1) the result of an inadequate intake of food due to anorexia or an incomplete diet, (2) the result of a loss of essential secretion or of food due to vomiting, diarrhea or external fistulas, (3) the result of a lack of decreased production of essential substances, and (4) the result of inadequate intestinal absorption. A lack of food intake by our patients seems undoubted. The failure of an alcoholic addict to admit this lack of proper nutrition is extraordinarily common, and it is small wonder that the incidence of allegedly poor diets as obtained in routine histories is as low as it is. It does seem noteworthy that the incidence of deficient diets was distinctly higher in those patients who had the complication of multiple peripheral neuropathy (although increased diligence on the part of the history taker may account for some of the difference). If one observes that which the patient actually eats, one reaches the conclusion that the overwhelming majority of patients entering this hospital with cirrhosis of the liver have been on a deficient diet. Whether it be cause or effect, many of those in the active stage have anorexia, nausea, "gas on the stomach" and vomiting. Some go on voluntary diets because of their gastrointestinal complaints, these diets usually are deficient in vitamins and proteins. Some have been drinking alcoholic liquors up to the hour of admission to the hospital. Others confess to the imbibition of inconsequential to tremendous amounts of these beverages in the past but sadly relate the cessation of such activity a few weeks or a few months previously because of the gastrointestinal symptoms which were produced. The direct toxic effect of alcohol as a factor in production of the peripheral neuropathy connected with cirrhosis thus appears to be ruled out, even as it has been ruled out under other circumstances.

Achlorhydria and hypochlorhydria are common in patients with cirrhosis. They are likewise commonly associated with various deficiency diseases. The significance of this or of possible decreased intestinal

25 Rich, A. R., and Hamilton, J. D. The Experimental Production of Cirrhosis of the Liver by Means of a Deficient Diet, *Bull. Johns Hopkins Hosp.* **66** 185-196 (March) 1940.

26 Wilbur, D. L., and Snell, A. M. Deficiency States Associated with Gastro-Intestinal Disease, *Am. J. Digest. Dis. & Nutrition* **4** 720-725 (Jan.) 1938.

absorption in cases of cirrhosis is difficult to evaluate. The same is true of the possibility that there is an inability on the part of the liver to metabolize thiamine adequately because of hepatic damage.

SUMMARY AND CONCLUSIONS

From an analysis of records of patients seen in the San Francisco County Hospital during the years 1928 to 1939 the following facts are noted:

Multiple peripheral neuropathy occurred in a high percentage of cases of cirrhosis of the liver.

There was a marked increase in the incidence of cirrhosis and probably of coexisting multiple peripheral neuropathy in the years 1933 to 1939.

A predominance of female patients and a higher percentage of early cirrhosis were observed in the cases in which neuropathy was present.

Alcoholism, general dietary deficiency and deficiency of thiamine intake were associated with both diseases.

The peripheral neuropathy of the patient with cirrhosis regressed when high vitamin therapy and, particularly, large amounts of vitamin B were administered.

The general condition of the patient with cirrhosis often improved at the same time.

Progress in Internal Medicine

BLOOD

REVIEW OF RECENT LITERATURE

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(Continued from page 1294)

GRANULOCYTOPENIA

A persual of the literature for 1939 dealing with granulocytopenia indicates that aminopyrine is now less important as an etiologic factor than it was several years ago. This is due to its decreased use, which undoubtedly is attributable to the knowledge that it may cause this serious condition. On the other hand, an increasing number of cases of granulocytopenia due to sulfanilamide and sulfapyridine are being reported. All evidence indicates that the most serious untoward effect of these two drugs is the production of granulocytopenia, which in a high percentage of the reported cases has terminated fatally. The exact incidence of granulocytopenia as a complication of sulfanilamide and sulfapyridine therapy is unknown, because doubtless many recognized cases are unreported, and in numerous others the syndrome is not identified. It apparently does not occur as frequently as the two other serious complications, namely, hemolytic anemia and gross hematuria resulting from deposition of crystals in the urinary tract. The granulocytopenia due to these substances does not appear to be associated with individual sensitivity of the person being treated but probably results from overdosage. A survey of the literature indicates that this complication rarely appears until a total of between 35 and 50 Gm. has been given, this amount is usually given over a period of twelve to fourteen days.

Observations in recent years have indicated clearly that gold preparations may cause granulocytopenia, but as such preparations have not been used extensively in the United States, their causal relation to the syndrome has not received widespread recognition. With the promising preliminary reports of the effectiveness of gold compounds in treating

rheumatoid arthritis, however, they appear likely to be utilized more frequently, and therefore an increased number of cases of granulocytopenia due to this cause is to be anticipated

The most important aspect of treatment of granulocytopenia is preventive. This means careful observation of patients who are receiving therapeutic agents which cause the condition and immediate withdrawal of these agents when the earliest manifestations of the disease appear. There is no specific therapy for the disease, but the observations of Jackson and of Tighe³⁵⁴ indicate that there is more evidence in favor of pentnucleotide than of any other type of medication. Sufficient data are not yet available for a satisfactory appraisal of the value of yellow bone marrow extract, but preliminary reports indicate that it is clearly worthy of further trial.

The article by Schultz³⁵⁵ on the present status of granulocytopenia, published in 1939, has an appealing interest, for it was his original publication in 1922 which directed the attention of physicians to the syndrome. After an interval of eighteen years, he again states his views about the disease in general. In his opinion the condition is characterized by a lack of resistance to infection which is attributable to decreased numbers or absence of neutrophils in the circulating blood. This permits the "bacteriologic parasites" of the person afflicted to involve the mucous membranes, the skin and the internal organs. Areas about the anus, the vaginal entrance and the prepuce may be involved. The most frequent finding, however, is an inflammatory diphtheria-like involvement of the throat, palate and lingual tonsil. There is frequently associated ulcerative or necrotic gingivitis. As the lesion of the gums is often the initial visible evidence of the disease, the dentist rather than the physician is often the first to see the patient.

Schultz emphasizes that the practitioner should be on the alert for the clinical characteristics of the disease, the more important of which he lists as follows: the greater incidence in women and in persons who are 40 years of age or more, the combination of gingivitis and tonsillitis and the usual general signs of severe sepsis. He likewise states that jaundice is a sign of the disease, but in our opinion this is not a commonly encountered manifestation of the syndrome in the United States. It is mentioned that the throat may give the appearance of diphtheria.

354 Jackson, H, Jr, and Tighe, T J G. Analysis of Treatment and Mortality of Three Hundred and Ninety Cases of Acute Angina, *New England J Med* **220** 729, 1939

355 Schultz, W. Der heutige Stand der Agranulozytosefrage, *Ztschr f ärztl Fortbild* **35** 647, 1938, Ueber eigenartige Halserkrankungen (a) Monozytenangina, (b) Gangraneszierende Prozesse und Defekt des Granulozytensystems, *Deutsche med Wchnschr* **48** 1495, 1922

but that this disease seldom occurs in persons over 40 years of age and that granulocytopenia is not common in children. It is emphasized that the syndrome of granulocytopenia may mask an underlying blood dyscrasia, such as leukemia or aplastic anemia.

Acknowledgment is made that aminopyrine plays a leading role in causation of the disease. This the author attributes to a constitutional sensitivity to the drug or to development of an anaphylactic state toward it after long usage. Other therapeutic agents, such as arsphenamine, bismuth compounds, gold preparations and, more recently, sulfanilamide, may less frequently be responsible for the production of the syndrome. Mention is made of the usual forms of treatment. Little comment is recorded regarding their efficacy except to say that transfusion with leukemic blood is not of much benefit and that stimulating doses of the roentgen ray are rarely used at present. The author issues an emphatic warning that surgical intervention is contraindicated and if employed may cause a relapse in a patient convalescing from the disease.

An excellent résumé of knowledge concerning granulocytopenia is presented by Reznikoff,³⁵⁶ in which he reviews data pertaining to the history, etiology, pathologic picture, symptoms and signs, blood picture, prognosis, differential diagnosis and therapy of the syndrome. It is stressed that the condition is a serious one and that in some series of cases there has been a high mortality rate. He believes that the causes of this condition are drugs, fatigue, menstruation and possibly infection. The most common drugs which may play an etiologic role are aminopyrine, dinitrophenol, organic arsenicals, gold salts, sulfanilamide and sulfapyridine. As many persons take these drugs with impunity, it must be assumed that granulocytopenia develops only when a person has an idiosyncrasy toward any one of them. He is in accord with the views of others that the essential lesion in the bone marrow in most cases is an arrest of myeloid maturation. It is his opinion that no specific remedy exists for the disease, although it is proper to administer any remedy which may help and will not harm a patient suffering from this condition. As in previous publications, he emphasizes that monocytosis is a favorable prognostic sign, which is a view shared by other observers.

Rosenthal and Vogel,³⁵⁷ in the very first sentence of their article, state that granulocytopenia in practically every case can be traced to an underlying sensitivity to certain drugs, such as aminopyridine, arsphenamine, dinitrophenol and, more recently, sulfanilamide. This rather dogmatic statement is probably in a large part correct but is difficult to

356 Reznikoff, P. Acute Neutropenia (Granulocytopenia), (Agranulocytosis), *Internat Clin* **3** 106, 1939.

357 Rosenthal, N, and Vogel, P. Agranulocytosis Caused by Sulfapyridine (Sulfanilamide Derivative) in Children, *J A M A* **113** 584 (Aug 12) 1939.

prove Nevertheless, for purposes of justifiable emphasis, it is a commendable one They consider that sulfapyridine has a toxicity for the bone marrow equal to or greater than that of sulfanilamide The chief purpose of their communication is to call attention to the danger of employing sulfapyridine over prolonged or intermittent periods unless frequent study is made of the blood picture In the few months prior to preparation of their article they had observed 3 cases of granulocytopenia in children, with 2 deaths, following administration of sulfapyridine They advise that use of the drug be discontinued if the leukocyte count falls to 3,000 or 4,000 per cubic millimeter and not resumed until the number of white blood cells returns to normal In their opinion, it is dangerous to give the drug over a long period continuously or intermittently in the presence of various types of infection, including pneumonia, in children According to these observers, the action of sulfapyridine on the bone marrow resembles that of neoarsphenamine to a great extent, as both cause rather definite changes which vary from arrest of maturation to a distinct, almost complete, suppression or hypoplasia of all elements The observation is again emphasized that monocytosis is a favorable prognostic sign It is advised that observations on the bone marrow of children who are receiving the drug are important Caution in its further administration should be used when the cellular content of the sternal marrow falls from a normal value of about 200,000 per cubic millimeter to less than 100,000 Attention is also directed to development of hemolytic anemia following sulfapyridine therapy, which usually manifests itself after a few days of therapy, whereas the development of granulocytopenia follows prolonged or intermittent use of the drug

In Keefer's³⁵⁸ opinion, granulocytopenia is the most serious complication of sulfanilamide therapy, as it is associated with such a high mortality rate The fact is emphasized that in no case has it occurred before the fourteenth to the sixteenth day after the beginning of treatment While exceptions to this statement will undoubtedly occur, it serves to emphasize the possibility that granulocytopenia is due to a high level of dosage of the drug rather than to the hypersusceptibility of a person to it Keefer also recognizes that the leukocyte count may fall after use of the drug has been discontinued for several days or when it is resumed after a preliminary withdrawal In his experience death has generally occurred within two or three days after the onset of granulocytopenia The importance is stressed of making repeated leukocyte counts in the cases of all persons who have been receiving the drug for a week or longer

358 Keefer, C S Sulfanilamide Its Mode of Action and Use in Treatment of Various Infections, *New England J Med* **219** 562, 1938

Dolgopol and Hobart³⁵⁹ report 2 cases of granulopenia and a like number of cases of leukopenia in a series of 35 cases of pertussis and pneumonia treated with sulfapyridine. In 1 case of granulopenia complicated by mild aplastic anemia the condition was fatal. The patient was a Negress aged 4 years with pertussis and lobar pneumonia. After 49 Gm of the drug had been given over a period of sixteen days, the red cell count was 2,770,000 per cubic millimeter, the value for hemoglobin 67 per cent and the leukocyte count 2,000 per cubic millimeter. No polymorphonuclear neutrophil cells were present in the blood films. At necropsy the bone marrow showed a slight decrease in the number of nucleated cellular elements in some areas but was not depleted as a whole. The patient in the second case was a Negro child aged 1 year, with pertussis and bronchopneumonia. At the end of fifteen days, during which time the total dose of the drug was 27 Gm, the red blood cell count was 4,900,000 per cubic millimeter, the value for hemoglobin 60 per cent and the white blood cell count 3,100 per cubic millimeter, with 5 per cent polymorphonuclear neutrophil cells. Recovery followed blood transfusions, pentnucleotide therapy and injections of liver extract. A third patient, a white girl aged 18 months with pertussis and bronchopneumonia, showed a white blood cell count of 4,200 per cubic millimeter, with 24 per cent polymorphonuclear neutrophils, after receiving 13 Gm of sulfapyridine in six days. An uneventful recovery followed withdrawal of the drug. A fourth patient was a white girl aged 10 months, with pneumonia and pertussis, the leukocyte count was 4,300 per cubic millimeter, with 14 per cent neutrophils, after an intake of 3 Gm of sulfapyridine in four days. As the concentration of the drug in the blood was only a trace, the therapy was not discontinued. Eight days later there was an increase in the number of white blood cells and neutrophils, and the patient recovered without complications.

That sulfapyridine may occasionally depress the bone marrow is not surprising, according to these authors. This is because the drug contains the benzamine group, which some consider to be responsible for the injurious action of a number of drugs on myeloid tissue. The leukopenia is attributed to an arrest in maturation of the leukopoietic elements, but at the same time the erythropoietic elements may be affected, as is indicated by reduction of the number of nucleated red blood cells in bone marrow smears.

Several pertinent questions are raised by these investigators relating to the action of sulfapyridine in producing changes in the peripheral

359 Dolgopol, V. B., and Hobart, H. M. Granulocytopenia (and Leukopenia) in Sulfapyridine (Sulfanilamide Derivative) Therapy, *J. A. M. A.* **113** 1012 (Sept. 9) 1939.

blood. They call attention to the fact that a relatively large total dose has usually been given to patients who show evidence of injury to the bone marrow. This evidence does not necessarily indicate that a high concentration in the blood results in deleterious effects. They are in accord with the view, which has hitherto been emphasized in relation to aminopyrine, that an individual sensitivity to sulfapyridine probably plays a role in the production of neutropenia in some cases. The possibility that a preliminary course of the drug may sensitize a person to subsequent doses must be considered, although the evidence favoring this mechanism of the production of toxic manifestations is not wholly convincing. They recognize that certain infections, such as those due to streptococci and typhoid fever, cause granulocytopenia independently of sulfapyridine therapy, but they conclude that pertussis can probably be excluded from the group of diseases producing such an effect. A warning is sounded against using excessively large amounts of sulfapyridine, and the recommendation of Whitby and others³⁶⁰ to keep the blood level at 8 mg per hundred cubic centimeters and to use 23 Gm of the drug per week for an adult is again emphasized. It is suggested that blood counts should be made twice weekly when sulfapyridine is being given and that they should be continued for two weeks after withdrawal of the drug. Such a recommendation is rational, but in our opinion it is one which is unlikely to be followed as frequently as is desired.

The case of a woman aged 22 who had fatal granulocytopenia following the taking of 35 Gm of sulfanilamide over a period of fifteen days is reported by Corr and Root³⁶¹. The patient had been ill with a severe infection of the throat for two weeks, and at the end of that time the white blood cell count was 800 per cubic millimeter, with 8 per cent neutrophils. Although slight improvement followed the use of pent-nucleotide and a blood transfusion, death occurred on the fifteenth day of the illness. The authors emphasize that 9 cases of fatal granulocytopenia apparently caused by sulfanilamide were reported prior to October 1938, together with a few in which recovery took place. It is their opinion, in which we concur, that an unknown number of deaths have probably occurred, some of which have been unrecognized and others of which have not been reported. Likewise, their surmise that many more cases are to be expected with the increasing use of this valuable drug is probably correct. Since it is recognized that such a serious com-

360 Whitby, L. E. H., and others, in *Discussion on Use of Sulphanilamide and Allied Drugs in Treatment of Human and Animal Diseases*, Proc Roy Soc Med **32** 349, 1939. Whitby, L. E. H. *Chemotherapy of Bacterial Infections* (Bradshaw Lecture), Lancet **2** 1095, 1938.

361 Corr, P., and Root, R. N. *Death from Granulocytopenia After Sulfanilamide Therapy*, J. A. M. A. **112** 1939 (May 13) 1939.

plication can result from the use of this drug, it becomes necessary to adopt some simple yet effective means of averting it. The suggestion that patients receiving sulfanilamide should have repeated examinations of the blood is not practical, for strict enforcement would curtail use of the drug and thereby cost more lives than could be saved by the prevention of deaths from agranulocytic angina. Even frequent examinations of the blood would not forestall all deaths from granulocytopenia, for the condition may not appear until several days after use of the causative agent has been discontinued. Two suggestions are made which are worthy of serious consideration, as follows: 1. Any patient with toxic symptoms should be denied further use of the drug or should be observed very carefully. 2. As granulocytopenia in all cases has developed after administration of 25 to 35 Gm of sulfanilamide or more, the practitioner can safely give up to 20 Gm of the drug before being concerned about granulocytopenia. In general we are in accord with this statement, for at present our knowledge seems to indicate that this serious complication follows ingestion of substantial amounts of the substance. The possibility, however, that it may result from a relatively small quantity when consumed by a person who has a specific sensitivity to it cannot be completely dismissed.

A case of granulocytopenia associated with a white blood cell count of 1,200 per cubic millimeter and no neutrophils in the circulating blood, developing in a patient with acute tonsillitis and pharyngitis in which the predominating organism was streptococci in short chains, is reported by Shullenberger³⁶². The condition became apparent after 52.3 Gm of sulfapyridine had been administered over a period of twenty-one days. Recovery followed withdrawal of sulfapyridine and administration of pentnucleotide. The author considers that it is impossible at present to state that sulfapyridine is less active than sulfanilamide in causing granulocytopenia. It is our estimate, wholly unsupported by facts, that when given in adequate doses one is as likely to cause granulocytopenia as the other.

Coxon and Forbes³⁶³ report the occurrence of granulocytopenia in a patient with typhoid fever. The condition developed after a total dose of 54 Gm of sulfapyridine in seventeen days. The authors state that while leukopenia is common with typhoid fever, granulocytopenia is rare in this association. We can confirm this statement, having

362 Shullenberger, W. A. Agranulocytosis Following Treatment of Bacterial Infections with Sulfapyridine. Case Report with Review of Literature, *J. Indiana M. A.* **32**: 415, 1939.

363 Coxon, R. V., and Forbes, J. R. Agranulocytic Angina Following Administration of M and B 693 (Sulfapyridine, Sulfanilamide Derivative), *Lancet* **2**: 1412, 1938.

observed such a case, in which the leukocyte count was 300 per cubic millimeter. It is the conclusion of the authors that in their case the granulocytopenia was due mainly to the sulfapyridine, although the typhoid fever may have been a contributing factor. They believe that sulfapyridine is probably less toxic than sulfanilamide but that in certain cases the former drug may cause injury to the leukopoietic system.

Myhre³⁶⁴ records a case of granulocytopenia associated with the therapeutic use of sulfanilamide and gives a bibliography including 25 other such cases. The patient, a woman, aged 53, with hypertension and an infection of the urinary tract due to *B. coli*, received 18.9 Gm of sulfanilamide in twenty-two days. The lowest white blood cell count was 2,200 per cubic millimeter, with 8 per cent myelocytes and 3 per cent "stuffs." Granulocytes with "segmented and staff" nuclei disappeared completely from the sternal bone marrow. A feature of this case was the appearance of large numbers of stipple cells in the circulating blood. This phenomenon most frequently occurs in cases of lead poisoning, but it may be present with many anemias, especially those due to increased destruction of blood. This may account for the appearance of stipple cells in this patient, although Myhre has found no previous mention in the literature of stippling after sulfanilamide medication. Of the 26 cases reported in the literature, 15 terminated fatally. The drug should be used with caution and never for more than seven to ten days at a time. Should a second course be required, the blood should be examined frequently, especially if there is a rise in body temperature. The treatment of granulocytopenia, according to Myhre, should begin with intramuscular administration of liver extract, and if this is unsuccessful nucleic acid preparations and blood transfusions should be given a trial.

A case of fatal granulocytopenia, with necropsy observations and a review of the literature dealing with this subject, is reported by Shecket and Price³⁶⁵. The patient, a 45 year old man, had a pulmonary infarction ten days after an operation for left indirect inguinal hernia. Sixty-four grams of sulfanilamide was administered in fifteen days. Cyanosis and dyspnea were noted in eight days, nausea and vomiting appeared in ten days and an erythematous macular rash developed thirteen days after initiation of therapy. Neutropenia was first observed on the sixteenth day, which was twenty-four hours after cessation of sulfanilamide therapy. Death occurred seven days after withdrawal of

³⁶⁴ Myhre, H. Sulphanilamide Agranulocytosis, *Acta med Scandinav* **99** 614, 1939.

³⁶⁵ Shecket, H. A., and Price, A. E. Fatal Granulocytopenia Following Administration of Sulfanilamide, *J. A. M. A.* **112** 823 (March 4) 1939.

the drug No other therapeutic preparations which are known to cause granulocytopenia were given Necropsy showed, among other observations, a myeloblastic arrest of the cells of the bone marrow These authors are not in accord with the belief of others that the action of sulfanilamide on the bone marrow is the result of a specific idiosyncrasy but are of the opinion that the quantity and prolonged use of the drug are the significant factors In support of this, they make the statement that the total dose of sulfanilamide in their own cases and the 9 similar cases then reported in the literature ranged from 35 to 64 Gm, with an average of 50 Gm These amounts were given over periods of from fifteen to thirty days, with an average of twenty-seven days The authors give the following pertinent advice, which may well be heeded by those who use the drug indiscriminately "The efficacy of sulfanilamide in a given condition should be demonstrated after 4 to 7 days If no improvement is noted within that period, the continued use of the drug is of doubtful value" Significant warning signals are cutaneous eruptions, hyperpyrexia, jaundice, reduction in the red blood cell count and either an abrupt rise or an abrupt fall in the number of white blood cells Although appearance of any one of these signs is not necessarily indicative of the toxic action of sulfanilamide, thoughtful consideration should be given to their appearance in a patient who is receiving the drug Emphasis is given to the growing opinion that granulocytopenia may be a late development in the course of sulfanilamide therapy, as is indicated by the fact that in 6 of the 10 cases reported in the literature the condition did not develop until from one to four days after the medication had been discontinued

Hall³⁶⁶ emphasizes that sulfanilamide may be responsible for two important abnormalities of the circulating blood It may cause an acute hemolytic anemia, which is the most common untoward effect but from which recovery usually occurs, or it may produce granulocytopenia, which has a sinister outlook According to this observer, of the 12 cases which had been reported in the literature up to that time, 8 terminated fatally Sulfanilamide possesses the benzene ring with the attached amino group, and in this respect it resembles aminopyrine, which is known to cause granulocytopenia in some persons The author reports the case of a boy aged 9 years who was treated for pneumonia with 45 Gm of the drug over a period of three weeks At the end of this time the white blood cell count was 1,900 per cubic millimeter, of which 12 per cent were neutrophils Later the count decreased to 850 cells per cubic millimeter, and no neutrophils could be found on exam-

³⁶⁶ Hall, B E Influence of Sulfanilamide on Blood, Proc Staff Meet, Mayo Clin 14 155, 1939

ination of the blood films. Death occurred despite treatment with pentnucleotide and liver extract given intramuscularly and yellow bone marrow extract (Stearns) given by mouth. When granulocytopenia is observed, it is recommended that use of the drug be stopped immediately, that fluids be forced by mouth and injected intravenously and that yellow bone marrow extract be given in daily doses of 50 to 200 capsules (each capsule containing 0.22 Gm). The results in his experience have been disappointing after use of pentnucleotide, liver extract and blood transfusions. A warning is given regarding the effect of sulfanilamide in the breast milk of mothers on nursing infants. Although the amount in breast milk is small and is unlikely to be harmful, it is known that the bone marrow of infants and young children is especially susceptible to toxins and chemical agents. Care should be taken, therefore, to observe the infant for toxic reactions.

According to Cutler and Crane,³⁶⁷ 9 cases of granulocytopenia following sulfanilamide therapy, with 2 recoveries, had been reported at the time their article was written. They include a personal communication from P. H. Long, who reports that 6 cases have occurred at the Johns Hopkins Hospital, with 2 recoveries. It is concluded that "undoubtedly" there is a greater incidence of this complication following sulfanilamide therapy than has been reported. The case of a young woman with acute bilateral pyogenic salpingitis who had granulocytopenia following administration of sulfanilamide is reported. After twenty-one days of therapy the white blood cell count fell to 2,600 per cubic millimeter, with 1 per cent polymorphonuclear cells. There was a coincident fall in the red blood cell count to 2,400,000 per cubic millimeter. The body temperature rose sharply, and the patient complained of sore throat, although there was only a slight infection of the fauces. Transient jaundice, persisting for over two days, was noted on the fourteenth day of treatment. Recovery followed multiple blood transfusions, pentnucleotide therapy and withdrawal of sulfanilamide. The authors recommend that patients receiving the drug should have daily erythrocyte and leukocyte counts. The possibility that the granulocytopenia may have been due to administration of other substances, such as aminopyrine, cannot be dismissed from a review of this article, as there is no statement concerning the administration of other drugs to the patient. Such a possibility is unlikely, however, as it is not common to observe hemolytic anemia associated with granulocytopenia due to aminopyrine. The authors emphasize that the course of events in this case is in accord with Keefer's³⁵⁸ statement that granulocytopenia

367 Cutler, I. L., and Crane, E. J. Agranulocytosis Caused by Sulfanilamide Recovered Case, *New England J. Med.* **221**: 231, 1939.

following sulfanilamide therapy has never been known to occur before the fourteenth day

Pearson³⁶⁸ reports the case of a 60 year old woman who had the syndrome of granulocytopenia with a white blood cell count of 600 per cubic millimeter and a neutrophil percentage of 2. The condition was recognized after a total dose of 34.5 Gm of sulfanilamide had been taken over a period of twenty-three days. A latent period of six days elapsed between omission of the drug and the appearance of warning symptoms. The author makes the suggestion that perhaps the duration of the treatment is of greater importance in relation to the development of granulocytopenia than is the total dose of the drug. The treatment in this case, which was unique but did not prevent a fatal outcome, consisted of a transfusion of 300 cc of citrated blood from a donor suffering with myeloid leukemia associated with a total white blood cell count of 120,000 per cubic millimeter.

Taub and Lefkowitz³⁶⁹ emphasize that sulfanilamide is a potential marrow poison the effect of which is cumulative. According to them, there is a causal relation between the size of the dose and granulocytopenia. They state that the fatal cases of granulocytopenia due to sulfanilamide followed a total dose varying from 38 to 94.5 Gm given in periods of from eighteen to forty days. Their own patient, who died, received 44 Gm in twenty-one days. Evidence of granulocytopenia was not discovered until three days after the medication was discontinued.

A patient with subacute bacterial endocarditis who was treated with sulfanilamide and succumbed with the symptoms of granulocytopenia is reported by Sailer³⁷⁰. A total dose of 282.6 Gm of the drug was given in twenty-three days. Examination of the bone marrow at necropsy showed alternating areas of aplasia and myeloid and lymphoid hyperplasia, with the former lesion predominating. Focal areas of necrosis were present in the intermediate zone of the liver. The author believes that these pathologic lesions were associated with sulfanilamide therapy and were not due to the original disease process.

According to the report of Gayus, Green-Armytage and Baker,³⁷¹ a woman aged 24 had granulocytopenia after receiving 39.5 Gm of

368 Pearson, H. E. S. Fatal Agranulocytosis After Sulfanilamide Therapy, *Brit M J* **1** 1031, 1939.

369 Taub, J., and Lefkowitz, L. Agranulocytic Angina Due to Sulfanilamide (Case), *New York State J Med* **39** 1659, 1939.

370 Sailer, S. Subacute Bacterial Endocarditis Treated with Sulfanilamide Resulting in Granulocytopenia and Death, *Am J Clin Path* **9** 269, 1939.

371 Gayus, I. K., Green-Armytage, V. B., and Baker, J. K. Puerperal Agranulocytosis Following Sulfanilamide Treatment. Record of Fatal Case, *Brit M J* **2**:560, 1939.

sulfanilamide in seventeen days, after a streptococcic infection following a normal delivery. The white blood cell count decreased to 850 per cubic millimeter, and no neutrophils were seen in a count of 150 cells. Death ensued despite use of 100 cc of pentnucleotide and administration of 1,100 cc of citrated blood by the continuous drip method. The authors warn that a complete examination of the blood should be made, even in the absence of symptoms of granulocytopenia, after 25 Gm of sulfanilamide has been given.

McNab and Parry³⁷² report the case of a woman aged 30 with puerperal fever. The white blood cell count was 1,400 per cubic millimeter with 8 per cent neutrophils after the patient had received 76 Gm of sulfanilamide in fourteen days. The red blood cell count fell to 2,590,000 per cubic millimeter, with a value for hemoglobin of 45 per cent. Recovery followed the use of 170 cc of pentnucleotide intramuscularly in doses of 10 cc, a blood transfusion and use of a liver extract (Campolon) and of ferrous sulfate.

A summary is given by Butt, Hoffman and Soll³⁷³ of the literature dealing with experimental production of granulocytopenia with aminopyrine in man and in animals. It is their opinion that the drug has a toxic action on the bone marrow in a majority of animals, but in only a small proportion are evidences of this reflected in the peripheral blood. In their experiments, 2 dogs which received 250.9 Gm and 255.5 Gm of aminopyrine respectively over periods of ten and one-half and nine months showed marked aplasia of the bone marrow. The authors consider that the action of the drug in the given doses is not unlike that of benzene and is somewhat selective, as destruction of myeloid elements precedes aplasia of the erythroblastic cells. The other dogs which were studied died of systemic toxic effects of aminopyrine before changes in the bone marrow were sufficiently marked to be unequivocal. The authors conclude that aminopyrine, in addition to its direct systemic toxic effect, has a selective action on the bone marrow. It is important to note that in the case of 1 of the 2 animals with severe aplasia of the bone marrow the leukocyte count was as low as 350 per cubic millimeter. It is the opinion of the authors that the toxic action of aminopyrine is far more frequent than Rawls's³⁷⁴ figures would indicate. Rawls expressed the opinion, estimated on clinical observations, that 1 to 2

372 McNab, D. J. N., and Parry, D. E. Agranulocytosis After Sulfanilamide. Recovery, *Brit M J* **2**: 565, 1939.

373 Butt, E. M., Hoffman, A. M., and Soll, S. N. Experimental Production of Neutropenia with Aminopyrine, *Arch Int Med* **64**: 26 (July) 1939.

374 Rawls, W. B. The Effect of Amidopyrine on Red, White and Polymorphonuclear Blood Cells of a Series of One Hundred Patients, *Am J M Sc* **192**: 175, 1936.

per cent of patients show susceptibility to the drug, as indicated by changes in the peripheral blood

Dardinski and Lyddane³⁷⁵ report the case of a man aged 65 who had fatal granulocytopenia after taken causalin (aminodimethylpyiazolonquinoline sulfonate) for relief of arthritis. The patient, who died on the same day on which he was admitted to the hospital, had been ill for a week with fever and with symptoms referable to the throat. The leukocyte count was 500 per cubic millimeter, with 29 per cent neutrophils, just before death.

Coventry³⁷⁶ records an interesting case of nonfatal granulocytopenia attributed to the therapeutic use of cinchophen in doses of $7\frac{1}{2}$ grains (0.48 Gm) every three hours for three weeks. This medicament, which was taken in combination with anacin (acetylsalicylic acid, acetophenetidin, quinine sulfate and caffeine), resulted in improvement in the rheumatic fever from which the patient was suffering. It is our opinion that the patient undoubtedly had granulocytopenia, for the leukocyte count decreased to 2,650 per cubic millimeter, and neutrophils were completely absent from the blood films. To prove that the granulocytopenia was due to cinchophen is another matter, difficult to demonstrate conclusively. It might have been, as the author suggests, that one of the other drugs which the patient was receiving caused the condition. Then, again, it must be considered that aminopyrine in some form, disguised by a trade name, may have been taken by the patient without the physician's knowledge. The possibility that cinchophen may have been the offending drug cannot be denied, on the other hand, the facts do not offer conclusive proof that this was the case.

Ives³⁷⁷ reports the case of a man aged 52 with fulminant necrotizing pharyngitis accompanied with complete granulocytopenia who recovered after the use of prontosil (now known as azosulfamide, disodium 4-sulfamidophenyl-2'-azo-7'-acetylamino-1'-hydroxynaphthalene-3',6'-disulfonate) and sulfanilamide. He considers that the angina and granulocytopenia were due to a hemolytic streptococcal infection and that the therapeutic preparations exerted a definite and specific action against the organism. Although recovery is attributed chiefly to this therapy, it is conceded that pentnucleotide and liver extract therapy were also of some benefit. Although this patient recovered, it is our opinion that the administration of sulfanilamide and similar drugs to a

375 Dardinski, V. J., and Lyddane, E. S. Agranulocytic Angina. Report of a Case Due to Causalin, *J. A. M. A.* **112** 134 (Jan. 14) 1939.

376 Coventry, W. D. Granulocytopenia, *Minnesota Med.* **22** 117, 1939.

377 Ives, R. F. Hemolytic Streptococcal Angina with Agranulocytosis Treated with Prontosil and Sulfanilamide, *Ann. Int. Med.* **12** 882, 1938.

patient with any prior damage to the bone marrow should be done with extreme caution, certainly excessive doses should be avoided

Granulocytopenia with a white blood cell count of 4,200 per cubic millimeter and 33 per cent neutrophils developed on the third day in a man aged 40 after an operation for a perforated appendix, as reported by Richmond³⁷⁸ Recovery followed intravenous injection of adenine sulfate in 2 Gm doses The author regards this substance as a non-toxic drug which is specific in stimulating myeloblastic activity in patients with granulocytopenia It is likely that this patient had severe sepsis with a poor response of the white blood cell-forming elements, as indicated by the total leukocyte count No positive statement is made, however, that sulfanilamide or sulfapyridine was not given

Jackson and Tighe³⁵⁴ present a comprehensive appraisal of the different forms of treatment administered in 390 cases of acute agranulocytic angina, based on a survey of the literature which has appeared since 1933 Although attempts to draw conclusions by this method may have its defects, they consider it the best available method of evaluating the various therapeutic agents so far advocated for this disease

The syndrome is delineated as an acute disease characterized by extreme leukopenia and granulopenia, the red blood cells and platelets are essentially unaltered, hemorrhagic manifestations are rare, an occasional immature white blood cell may appear in the blood at the height of the disease, there is no enlargement of the liver and spleen, and no lymphadenopathy is present other than that which is due to local sepsis Death may terminate the illness within thirty-six hours of the onset, and recovery, if it takes place, usually occurs within two weeks It is generally agreed, according to the authors, that many cases are caused by aminopyrine, dinitrophenol and "similar compounds", they consider that the characteristic lesion in the bone marrow is arrest of maturation of the granular white cell series at the myeloblast stage It is properly emphasized that the disease must be differentiated from aleukemic leukemia, aplastic anemia, leukopenia due to overwhelming sepsis and chronic leukopenia due to diverse causes In an effort to evaluate accurately the effects of treatment, all patients who received inadequate treatment, as well as those who recovered when similar therapy was given, were eliminated The death rate in these two groups of patients was 73 per cent, which is the same as that observed with patients who received no specific therapy whatever

378 Richmond, E L Granulocytopenia Following Surgical Sepsis and Treated with Adenine Sulfate, *New England J Med* **221** 267, 1939

These authors, after a survey of the literature, present the following conclusions concerning the effectiveness of various forms of therapy in the disease

	Mortality, Per Cent
1 No specific therapy	70-80
2 Transfusions	74
3 Stimulating doses of roentgen ray	67
4 Parenteral liver extract	62
5 Pentnucleotide	35
6 Adenine sulfate	20
7 "Leukocytic cream"	17
8 Yellow bone marrow extract	10

The authors conclude that neither roentgen therapy nor blood transfusion alters the mortality. Likewise, from these figures liver extract seems to be ineffective. Treatment with yellow bone marrow extract, leukocytic cream and adenine sulfate is associated with a low death rate and accordingly deserves a further trial. On account of the small number of patients who have received these forms of therapy, however, it is not possible to appraise their ultimate value at present. As the mortality in 85 cases treated with pentnucleotide was 35 per cent, they conclude that use of this drug in doses of 40 cc daily "is the most promising form of specific therapy in this disease."

To us, from a consideration of the literature and from personal experience, it would appear that the most effective management of patients with agranulocytic angina is as follows

- 1 Simultaneous administration of pentnucleotide intramuscularly in doses of 40 cc daily and of yellow bone marrow extract orally in daily doses of 300 to 500 Gm

- 2 Treatment of the lesions of the mouth and throat with bland saline irrigations and avoidance of surgical intervention in these areas during the acute process

- 3 Prohibition of all drugs, such as aminopyrine, sulfanilamide and allied substances, which are known to cause granulocytopenia

- 4 Use of blood transfusions for the occasional patient who has had anemia prior to development of granulocytopenia or who shows anemia during the course of the disease

HODGKIN'S DISEASE, LYMPHOSARCOMA AND LYMPHOMATOID DISEASES

Ewing³⁷⁹ classifies tumors of the lymph nodes as lymphadenoma (multiple giant follicular lymphadenoma, Brill's disease, gastrointestinal

³⁷⁹ Ewing, J. General Pathology of Lymphosarcoma. Bull. New York Acad. Med. 15: 92, 1939

pseudoleukemia), lymphocytoma (systemic pseudoleukemia, lymphocytic leukemia, malignant disseminating lymphocytoma, plasmacytoma, solitary lymphoma), and reticulum cell lymphosarcoma (large round cell lymphosarcoma affecting many regions and organs) Gastrointestinal pseudoleukemia is a peculiar systemic disease producing myriads of small lymphomas in the mucosa from the mouth to the anus, without ulceration, and extending to many chains of lymph nodes and the spleen The course is steadily progressive and active, with fever, anemia, diarrhea, emaciation, peritonitis and death within a few months or years Structurally, the growth shows well formed lymph follicles without the diffuse growth of malignant tumors The cause is unknown

An excellent critical review of the present status of Hodgkin's disease is presented by Krumbhaar³⁸⁰ It is too complete to review here, and the article should be studied by any one working with Hodgkin's disease In a general review of reticulum cell sarcoma and giant follicle lymphoma (grouped as malignant lymphoma), Jackson³⁸¹ points out that besides the lymph nodes, the spleen, liver, pancreas, gastrointestinal tract, bones, skin, lung, heart, nasopharynx, breast, ovary and testicle may be involved (in descending order) Involvement of the central nervous system is not rare Surgical intervention may be of value in selected cases of Hodgkin's disease when the process is limited to accessible glands Roentgen therapy gives the best responses, but the danger of primary swelling of the glands producing pressure symptoms and of toxemia from destruction of large amounts of tissue must be kept in mind Hodgkin's disease is divided into Hodgkin's lymphoma, Hodgkin's granuloma and Hodgkin's sarcoma, with prognosis decreasing in hopefulness in the order named

Epstein³⁸² comments on the fact that Hodgkin's disease is less frequent and less malignant in women than in men Glandular activity may possibly exert a restraining influence on the condition

In cases of lymphogranulomatosis and of Banti's disease, Schousboe³⁴⁵ interprets the anemia, leukopenia, thrombopenia, hyperplasia of the bone marrow and immaturity of the leukocytes as evidences of splenic inhibition, remediable by splenectomy

Baker and Mann³⁸³ report a summary of the clinical findings in 65 cases of Hodgkin's disease

380 Krumbhaar, E. B. The Present Status of Hodgkin's Disease, in A Symposium on the Blood and Blood-Forming Organs, Madison, Wis., University of Wisconsin Press, 1939, p. 148

381 Jackson, H. Hodgkin's Disease and Allied Disorders, New England J. Med. **220** 26, 1939

382 Epstein, E. Sex as a Factor in the Prognosis of Hodgkin's Disease, Am. J. Cancer **35** 230, 1939

383 Baker, C., and Mann, W. N. Hodgkin's Disease. A Study of Sixty-Five Cases, Guy's Hosp. Rep. **89** 83, 1939

A contribution of some significance is that of Parsons and Poston³⁸⁴ concerning the similarity of the histologic structure of glands in cases of Hodgkin's disease and in cases of chronic brucellosis. *Brucella* organisms were cultured from lymph nodes in which the histologic picture was identical with that of Hodgkin's disease. The glands of a patient with chronic brucellosis may show complete destruction of the original architecture of the lymph node, pronounced eosinophilia, focal scarring, production of large pale mononuclear cells and production of Dorothy Reed cells. Lesions of chronic brucellosis may be associated with negative agglutination reactions, negative brucellergen reactions and negative or low phagocytic indexes, but the cultures yield the organisms.

Rabson's³⁸⁵ description of the granulomas associated with brucellosis in man is perfectly compatible with Parson and Poston's observations, and the relation of brucellosis and Hodgkin's disease is a subject for further study.

Uhlenhuth and Wurm,³⁸⁶ although unable to transmit Hodgkin's disease to animals, regard it as an infection. They do not consider tuberculosis, streptothrix, diphtheroid bacilli or the elementary bodies of Gordon and Gow as etiologic factors. They confirm the work of others, who have shown that a constituent of the eosinophils is the cause of a positive result in Gordon's test.

Pittaluga³⁸⁷ concludes that differences between megakaryoblasts, megakaryocytes and cells of Sternberg make it unlikely that Hodgkin's disease represents a systemic metaplasia of megakaryocytes.

Scott and Robb-Smith³⁸⁸ describe a new syndrome which they call histiocytic medullary reticulosis. This condition, formerly grouped with Hodgkin's disease, is characterized by fever, wasting and generalized lymphadenopathy associated with splenomegaly, hepatomegaly and, in the final stages, jaundice, purpura, anemia and profound leukopenia. On postmortem examination a systematized hyperplasia of histiocytes actively engaged in the phagocytosis of erythrocytes is observed. The

384 Parsons, P. B., and Poston, M. A. The Pathology of Human Brucellosis. Report of Four Cases with One Autopsy, *South M. J.* **32** 7, 1939.

385 Rabson, S. M. Pathologic Anatomy of Human Brucellosis, *Am. J. Clin. Path.* **9** 604, 1939.

386 Uhlenhuth, P., and Wurm, K. Untersuchungen zum Problem der Hodgkinschen Krankheit. I. Experimentelle Untersuchungen zur Ätiologie der Hodgkinschen Krankheit, *Ztschr. f. d. ges. exper. Med.* **105** 205, 1939.

387 Pittaluga, G. Cellules de Sternberg et megakaryocytes, *Sang* **13** 833, 1939.

388 Scott, R. B., and Robb-Smith, T. Histiocytic Medullary Reticulosis, *Lancet* **2** 194, 1939.

authors describe 4 cases and summarize the details of 6 cases reported by others. The course is rapid, with death in from six to thirty-two weeks (average, fifteen weeks).

Velasco Montes³⁸⁹ notes that the bone marrow is involved in only about one half of the patients with Hodgkin's disease and therefore that gland puncture has an advantage over sternal puncture as a diagnostic procedure. Classification of "adenograms" is based on the predominance of certain cell types. Glandular puncture is less annoying to the patient than exploratory excision (removal of a biopsy specimen), there is less danger of a flare-up of the disease process, and the procedure may be repeated as often as desired. Interpretation of the cellular material is often difficult, however, especially after roentgen therapy. When there is much sclerosis or when glands are not accessible, splenic puncture may be of diagnostic value.

Changes similar to those resulting from injection of extracts of lymph nodes from patients with Hodgkin's disease or from leukocytic cream of human blood follow injection of monkey bone marrow extract intracerebrally into rabbits. Encephalopathy develops, with ultimate necrosis (King³⁹⁰).

Plá, Pérez Sánchez and Granotich³⁹¹ consider that a virus is present in cases of malignant lymphogranuloma which may cause neurologic symptoms. Lymph nodes or metastatic nodules may give rise to symptoms by compression of the lateral columns of the spinal cord, the brain or the nerve roots.

Liebegott³⁹² obtained a positive result from a Gordon test of lymphogranulomatous tissues only when a considerable number of eosinophils were present.

The occurrence of eosinophilic hyperleukocytosis in association with Hodgkin's disease is reported by Major and Leger³⁹³. The leukocyte count reached a maximum of 169,000 per cubic millimeter, with 95 per cent eosinophils. The absence of myelocytes and splenomegaly and the

389 Velasco Montes, F. Ueber die hamatologische Diagnose der Lymphogranulomatose (Hodgkinsche Krankheit), *Munchen med Wchnschr* **86** 255, 1939.

390 King, L. S. Encephalopathy Following Injections of Bone Marrow Extract, *J Exper Med* **70** 303, 1939.

391 Plá, J. C., Perez Sanchez, A., and Granotich, J. P. Neurolymphogranulomatous Syndromes, *Arch urug de med, cir y especialid* **14** 513, 1939.

392 Liebegott, G. Histologisches Bild und Gordon-Test bei der Lymphogranulomatose, *Verhandl d deutsch path Gesellsch* (1938) **31** 459, 1939, Untersuchungen zum Problem der Hodgkinschen Krankheit II. Ueber die Beziehungen zwischen histologischem Bild und Gordon-Test bei Lymphogranulomatose, *Ztschr f d ges exper Med* **105** 241, 1939.

393 Major, R. H., and Leger, L. H. Marked Eosinophilia in Hodgkin's Disease, *J A M A* **112** 2601 (June 24) 1939.

positive evidence of Hodgkin's disease from biopsy of material from a lymph node differentiated this condition from leukemia

In Dunn's ³⁹⁴ case of lymphosarcoma removal of the affected inguinal nodes and high voltage roentgen therapy were followed by no evidence of recurrence for over three years

Of sarcomatous growths of the stomach observed at the Mayo Clinic, Madding ³⁹⁵ found 30 per cent to be lymphosarcoma, 32 per cent round cell sarcoma, 8 per cent malignant lymphocytoma and 11 per cent Hodgkin's disease Metastatic lesions (65 to 70 per cent) occurred most frequently in the regional (gastric) lymph nodes The average age of the patients was 46 years, with a preponderance of men (6 1) Pain was the most common symptom, being generalized either in the abdomen or in the epigastrium Free hydrochloric acid was absent in the gastric contents of 67 per cent of the patients, and blood was not found as frequently as in cases of carcinoma The lesion is very radio-sensitive, but operation is advocated whenever possible

In describing 5 cases of lymphosarcoma of the stomach, Taylor ³⁹⁶ comments on the difficulty of making a clinical diagnosis, as there are no distinctive symptoms and no characteristic roentgen picture Complete surgical removal of the lesion is desirable but not always feasible Roentgen therapy has produced complete clinical remissions lasting up to eight years Of 147 patients with primary lymphosarcoma of the stomach mentioned previously in the literature, 13 are living and well five to twenty-two years after discovery of the lesion (A bibliography of articles describing these cases, from 1893 to 1937, is appended) Cases of lymphosarcoma of the stomach are reported in Cabot cases 24501 and 25011,³⁹⁷ and a primary isolated case of Hodgkin's disease of the stomach is described by Avent ³⁹⁸ In Martin, Denise and Muller's case ³⁹⁹ lymphosarcoma of the small intestine occurred in a 6 year old child

394 Dunn, G R Lymphosarcoma of Inguinal Glands Case Report, Minnesota Med **22** 284, 1939

395 Madding, G F Lymphosarcoma of the Stomach with Particular Reference to the Reticulum Cell Variety, Proc Staff Meet, Mayo Clin **14**:202, 1939

396 Taylor, E S Primary Lymphosarcoma of Stomach, Ann Surg **110** 200, 1939

397 Lymphosarcoma of Stomach, Cabot Case 24501, New England J Med **219** 961, 1938 Hodgkin's Sarcoma of Stomach, Duodenum and Jejunum, Cabot Case 25011, *ibid* **220** 31, 1939

398 Avent, C H Primary Isolated Lymphogranulomatosis (Hodgkin's Disease) of Stomach Report of a Case, Arch Surg **39** 423 (Sept) 1939

399 Martin, J F, Denise, H, and Muller, B Un cas de sarcome lymphoblastique de l'intestin grêle chez un enfant de six ans, Lyon méd **162** 393, 1938

Bernard⁴⁰⁰ comments on the periodicity of the fever associated with Hodgkin's disease, comparing it with that observed with undulant fever and tuberculosis. In Townsend and Braunstein's⁴⁰¹ case of Hodgkin's disease there was severe macrocytic anemia (mean corpuscular volume, 146 cubic microns). The secretion of hydrochloric acid was not abnormal. There was a reticulocyte response to liver extract. At autopsy, gross infiltration of the bone marrow with Hodgkin's tissue was noted. There was no bilirubinemia, and no neurologic changes were observed. Possible causes were a prolonged dietary deficiency or involvement of the liver.

Behrend's⁴⁰² patient had a Hodgkin's tumor of the anterior portion of the mediastinum and chest wall. Roentgen therapy caused diminution in size of the mass, and the tumor was removed surgically. No recurrence was noted in eighteen months. In Harrell's case⁴⁰³ there was invasion of the pericardium and of the gallbladder. Eight cases in which there were pericardial lesions had been reported previously. Hardin's⁴⁰⁴ patient had a massive collapse and cavitation of the lungs. In Pfahler's⁴⁰⁵ case of mediastinal glandular tuberculosis in an adult there were some features requiring differentiation of the condition from Hodgkin's disease. The patient recovered. In Kravitz's⁴⁰⁶ case the disease involved the eyelid.

A case of aleukemic lymphosarcoma cell leukemia in a 64 year old man is described by Varadi.⁴⁰⁷ Data obtained by sternal and lymph gland aspiration showed lymphoblastomatous proliferation, with 21 to 66 per cent of the cells in the peripheral blood of lymphoid origin and a total leukocyte count ranging from 5,500 to 15,500 per cubic millimeter.

Giordano's⁴⁰⁸ series of patients with Hodgkin's disease included 65 men and 37 women ranging from 11 to 80 years of age (the majority

400 Bernard, A. La fièvre ondulante dans la maladie de Hodgkin, *Bruxelles-med* **19** 288, 1939.

401 Townsend, S. R., and Braunstein, A. L. Hyperchromic Macrocytic Anemia in Association with Hodgkin's Disease, *Canad. M. A. J.* **41** 254, 1939.

402 Behrend, M. Hodgkin's Disease of Anterior Mediastinum and Anterior Chest Wall, *Am. J. Surg.* **45** 348, 1939.

403 Harrell, G. T. Hodgkin's Disease with Invasion of Pericardium and Gall Bladder. Review of Literature and Report of Case with Autopsy, *Arch. Path.* **28** 58 (July) 1939.

404 Hardin, B. L. Case of Hodgkin's Disease with Massive Collapse and Cavitation of Lung, *Am. J. M. Sc.* **197** 92, 1939.

405 Pfahler, G. E. Mediastinal Glandular Tuberculosis in Adult Resembling Hodgkin's Disease. Recovery of Case, *Am. J. Roentgenol.* **41** 742, 1939.

406 Kravitz, D. Hodgkin's Disease of the Lid. Report of Case, *Arch. Ophth.* **21** 844 (May) 1939.

407 Varadi, S. Reticulosarcome leucémique (reticulo-lympholeucosarcomatose), *Sang.* **13** 1, 1939.

408 Giordano, G. I nostri risultati nel trattamento radiante del linfogranuloma, *Radiol. med.* **26** 429, 1939.

between 21 and 30) The average treatment consisted of administration of 250 r at a time Resistant tumors were treated with radium For cases of diffuse involvement, "superteleoroentgen therapy" was employed, with irradiation of the whole body for two hours at intervals of four or five days, 25 r being used at each treatment The results appear best when the treatment is given early in the course of the disease The duration of life in Giordano's series was more than three years in 45 cases and more than five years in 21 cases

Craver⁴⁰⁹ notes that Hodgkin's disease, lymphosarcoma and leukemia in children under 15 years of age have many points in common with the conditions in adults Leukemia is nearly always acute and rapidly fatal and cannot be treated with roentgen therapy For children with Hodgkin's disease the prognosis for palliation and length of survival is better than with lymphosarcoma or leukemia

Marcellus⁴¹⁰ reports the curious coincidence of varicella and herpes in a patient with Hodgkin's disease

In Randall's⁴¹¹ case of Hodgkin's disease, extensive abdominal growths with deepening jaundice followed seven years after mediastinal involvement The mediastinal glands became hyalinized Rae's⁴¹² patient, a man of 51, had intracranial deposits, convulsive seizures and an irregular temperature not characteristic of the Pel-Ebstein syndrome There was marked pruritus Browder and DeVeer⁴¹³ described 6 patients in whom lymphomatoid lesions involved the epidural space These included lymphosarcoma (small and large cell types), giant follicular lymphadenoma, reticulum cell sarcoma, Hodgkin's disease, and multiple myeloma

In Bomze and Kirschbaum's⁴¹⁴ case a 12 year old boy died of malignant thymoma (lymphosarcoma) There was no involvement of lymph glands and no leukemic infiltration of the other organs, and the blood picture was not abnormal The tumor was radiosensitive, but death was caused by compression of the trachea and heart

409 Craver, L F Lymphomas, Leucemias and Allied Disorders in Children, *J Pediat* **15** 332, 1939

410 Marcellus, M B Hodgkin's Disease with Herpes Zoster and Varicella, *Northwest Med* **38** 279, 1939

411 Randall, E, Jr Internal Hodgkin's Disease, *Texas State J Med* **34** 751, 1939

412 Rae, A S L Clinical Record A Case of Hodgkin's Disease with Cutaneous and Cerebral Manifestations, *Edinburgh M J* **46** 400, 1939

413 Browder, J, and DeVeer, J A Lymphomatoid Diseases Involving the Spinal Epidural Space A Pathologic and Therapeutic Consideration, *Arch Neurol & Psychiat* **41** 328 (Feb) 1939

414 Bomze, E J, and Kirschbaum, J D Lymphosarcoma of Mediastinum (Malignant Thymoma) A Clinical and Pathological Study with Case Report of a Child, *J Lab & Clin Med* **24** 928, 1939

Dyes ⁴¹⁵ and Horster ⁴¹⁶ present cases of Hodgkin's disease associated with pregnancy Taylor and De Ome ⁴¹⁷ found that feeding wheat germ oil to chickens had no appreciable effect on the incidence, type or age of onset of lymphomatosis

For Hodgkin's disease, Gilbert ⁴¹⁸ recommends roentgen therapy only when there is a specific indication, and such therapy should be repeated only when necessary He deprecates the so-called maintenance or prophylactic treatment as superfluous or even detrimental Radium may produce a symptomatic remission of Hodgkin's disease, with reduction in size of deep-seated lymph nodes in the chest Sayago ⁴¹⁹ found that 160 mg of radium at a distance of 6 to 7 cm from the skin was a sufficiently strong source of radiation to accomplish excellent results The cutaneous lesions of lymphoblastoma may be treated with irradiation (Pett ⁴²⁰)

In Blatt and Page's ⁴²¹ patient (a 38 year old man), a lymphosarcomatous mass involved the kidneys, renal vessels, ureters, abdominal aorta, inferior vena cava and adrenal glands Hypertension (systolic blood pressure, 204 mm, diastolic, 110 mm) was a marked symptom and probably was the result of constriction of the renal arteries simulating the production of hypertension by the Goldblatt clamp

In 5 cases of follicular lymphoblastoma described by Mayer and Thomas,⁴²² 2 patients showed changes limited strictly to the follicles, but in 1 of these the disease ran a malignant clinical course Three of the patients showed invasion of the pulp by germinal center cells, in 2 of these the condition ran a malignant clinical course, while the third responded well to roentgen therapy Four other cases are described in which there were general or local lymphadenopathy, splenomegaly (tumor cells in malpighian bodies), lymph nodes showing diffuse

415 Dyes, O Lymphogranulomatose und Schwangerschaftsunterbrechung, Munchen med Wchnschr **86** 605, 1939

416 Horster, H Lymphogranulomatose und Schwangerschaft, Deutsche med Wchnschr **65** 680, 1939

417 Taylor, L W, and De Ome, K B Failure of Wheat Germ Oil to Prevent Lymphomatosis in Chickens, J Am Vet M A **95** 73, 1939

418 Gilbert, R Radiotherapy in Hodgkin's Disease (Malignant Granulomatosis) Anatomic and Clinical Foundations, Governing Principles, Results, Am J Roentgenol **41** 198, 1939

419 Sayago, C Radium Therapy in Hodgkin's Disease Report of a Case, Am J Roentgenol **42** 888, 1939

420 Pett, R G Irradiation of Cutaneous Manifestations of Lymphoblastoma, Pennsylvania M J **42** 387, 1939

421 Blatt, E, and Page, I H Hypertension and Constriction of Renal Arteries in Man Report of Case, Ann Int Med **12** 1690, 1939

422 Mayer, S, Jr, and Thomas, H M, Jr Follicular Lymphoblastoma and Related Form of Lymphosarcoma, Bull Johns Hopkins Hosp **64** 315, 1939

infiltration with lymphoblastic cells and a normal blood picture except for a moderate degree of anemia and a rapidly fatal course. These conditions constitute a separate syndrome.

LEUKEMIA

Biologic and Etiologic Aspects—Forkner⁴²³ summarizes the hematologic criteria in the differentiation of acute leukemias as follows: 1. The dominant leukocytes (85 per cent) are of uniform and immature type. 2. Leukocytosis may be absent, and leukopenia with fluctuations in the count may characterize the disease. 3. Thrombopenia is present. 4. Prolonged coagulation and bleeding times are observed. 5. There is rapidly developing anemia. The supravital technic is of aid in the diagnosis of monocytic cells. In cases of aleukemic myelogenous leukemia, roentgenograms of the skull, pelvis and femurs may show multiple erosions.

In a series of 20 cases of myelogenous and lymphatic leukemias, Davis and Fitz-Hugh⁴²⁴ found an incidence of 35 per cent achlorhydria after administration of alcohol and histamine. Of the 20 patients, 7 had a smooth tongue, and in 4 the papillae were few. There was no correlation between achlorhydria, glossitis, anemia and neurologic disturbances in the group. Liver therapy appeared to have no effect on the anemia of these patients.

Moon⁴²⁵ suggests the classification of leukemic and related conditions on the basis of (1) lymphoid, myeloid or reticuloendothelial ("retothelial") reaction, (2) the presence or absence of abnormal numbers of the pathologic cells in the blood, and (3) the presence of the same type of cell somewhere in the body.

An anonymous author,⁴²⁶ in evaluating Engelbreth-Holm's⁴²⁷ review (with an extensive bibliography) on leukemia, summarizes the available data as follows. The predisposing factors in cases of leukemia appear to be heredity, an external environmental factor (irritation) and a virus. While about 25 human families are known in which more than 1 case of leukemia occurring in near relatives has been recorded, pure strains of mice have been bred in which the incidence of leukemia was

423 Forkner, C. E. Monocytic Leukemia and Subleukemic (Aleukocytic or Aleukemic) Leukemia, in *A Symposium on the Blood and Blood-Forming Organs*, Madison, Wis., University of Wisconsin Press, 1939, p. 126.

424 Davis, C. L., and Fitz-Hugh, T. Achlorhydria in the Leukemias, *Am J M Sc* **197**: 763, 1939.

425 Moon, V. H. Practical Classification of Leukemic and Related Conditions, *Am J Clin Path* **9**: 100, 1939.

426 Is Leukaemia a New Growth? editorial, *Brit M J* **2**: 1147, 1939.

427 Engelbreth-Holm, J. Ergebnisse der Leukoseforschung der letzten Jahre, *Ergebn d inn Med u Kinderh* **56**: 267, 1939.

90 per cent In other strains the disease has been bred out so that it appears in only about 1 per cent Radium, roentgen rays, tar and carcinogenic hydrocarbons have been reported as causing leukemia In fowls, spontaneous leukemias can be transmitted to healthy birds by cell-free filtrates, and the virus acts much more rapidly than irritants Sarcoma and leukemia have been produced by the same filtrable agent

Jackson ⁴²⁸ points out that leukemia in individual cases may deviate sharply from the classic type and that other pathologic conditions, some of them curable, may give rise to a leukemoid blood picture In 2 cases of lymphatic leukemia, in 1 of nine and in the other of twelve years' duration, there were very few symptoms McGavran's case, in which there was leukemia of at least twenty-five years' duration, is cited Sudden death from massive hemorrhage may occur from myelogenous leukemia in patients who are otherwise progressing satisfactorily Aleukemic leukemia without characteristic physical findings or with symptoms of arthritis or acute abdominal disease may make the diagnosis difficult Dramatic remissions may occur during the course of the disease Miliary tuberculosis, carcinoma and myelosclerosis with myeloid metaplasia may give rise to leukemoid blood pictures

Tissue autolysis with production of leukemia in chickens, dogs, monkeys, hogs, goats and sheep was induced by intravenous injection of living and heat-killing species of paratyphoid and typhoid bacilli and by injection of freshly emulsified, desiccated and autolyzed homologous tissues in the chicken, dog, monkey and goat Benzene, phenol, xylene and suboxidation were effective in the chicken Leukemia is considered as due to self-perpetuating tissue autolysis (Emmel ⁴²⁹)

A paper of unusual interest in connection with the causation of leukemia is that of Wearn, Miller and Heinle ⁴³⁰ These authors found that there is a substance in the urine of patients with leukemia which, when extracted by adsorption on kaolin (purified native hydrated aluminum silicate) from acid solution and eluted with alcohol, produces, on injection into guinea pigs, changes in the hemopoietic organs suggestive of the type of leukemia from which the urine was taken Thus, there were marked hyperplasia of the bone marrow and metaplasia of myeloid cells in other parts of the reticuloendothelial system when the urine of patients with myelogenous leukemia was used, but when that

428 Jackson, H, Jr The Protean Character of the Leukemias and of the Leukemoid States, *New England J Med* **220** 175, 1939

429 Emmel, M W The Nature of Leukemia A New Fundamental Principle Leading to the Development of Specific Disease, *J Am Vet M A* **46** 316, 1938

430 Wearn, J T, Miller, F R, and Heinle, R W Proliferation of the Reticulo-Endothelial System Induced by Extracts of Urine from Patients with Leukemia, *Tr A Am Physicians* **54** 278, 1939

from patients with lymphatic leukemia or multiple myeloma was injected hyperplasia of the lymphoid elements was found. Extracts from urine of normal persons or of urine from patients with several other diseases did not produce this hyperplasia. As the extracts retained their activity after submission to a p_H of 1.5 and after boiling for five minutes, the authors conclude that the active substance probably was not a virus.

In 19 cases of chronic or subacute myelogenous or lymphatic leukemia, Morelli and D'Ambrosio⁴³¹ found that the indirect van den Bergh reaction was positive, the icteric index above normal, the resistance of the red blood cells moderately increased and, frequently, the urobilin content of the urine increased. Since all these findings agree with an increased hemolytic process, the authors advance the hypothesis that the anemia associated with leukemia is a hemoclastic phenomenon. It is not due to an aplastic process but to increased hemolytic activity of the spleen, profoundly altered by the lymphatic or myeloid metaplasia of the splenic tissue. The endocrine, leukopoietic and metabolic disturbances common to dysthyroidism and leukemia suggest to Marques⁴³² a common pathogenic factor for the two conditions. Lesions of the thyroid of the type of colloidal goiter were observed in 2 cases at autopsy.

Gerundo,⁴³³ who favors the virus theory of leukemia, views the condition as a hyperplastic process involving the hemopoietic organs. Leukopenia is explained as representing a hyperfunction of the inhibitory action of the spleen on the growth and delivery of cells from the bone marrow and the hemohistioblastic nests.

Israels⁴³⁴ points out that lymphatic leukemia may exist in the absence of some classic signs but that lymphocytosis of the bone marrow (on sternal puncture) is diagnostic. Hynes's⁴³⁵ observations bear this out, especially in the diagnosis of leukemia in the absence of peripheral leukocytosis. In the presence of leukemia the marrow is extremely cellular, with a great increase in the number of primitive leukocytes and a "maturation defect" in the red blood cells resulting in macrocytosis. The latter process differs from that in cases of pernicious anemia in that there is no premature hemoglobinization of the erythroblasts.

Voth⁴³⁶ points out that it is often difficult to differentiate between granulocytopenia and aleukemic leukemia. There is often a marked

431 Morelli, A., and d'Ambrosio, L. Il ricambio emoglobinico nelle leucemie, *Haematologica* **20** 253, 1939.

432 Marques, A. A glandula tiroide e as leucemias, *Jorn dos clin* **20** 17, 1939.

433 Gerundo, M. Acute Leukemia and Erythremia, *J Kansas M Soc* **40** 460, 1939.

434 Israels, M. C. G. Lymphatic Leukaemia. Value of Sternal Puncture in the Diagnosis of Atypical Cases, *Brit M J* **2** 1132, 1939.

435 Hynes, M. Sternal Puncture, *Lancet* **1** 1373, 1939.

436 Voth, G. Granulocytopenie und Leukämie, *Folia haemat* **62** 184, 1939.

discrepancy between the state of the cells in the blood stream and in the bone marrow. Granulocytopenia and aleukemic leukemia may be the first stage in a process affecting the bone marrow, which in some persons evolves into the second stage, acute myeloblastic leukemia.

Scott⁴³⁷ characterizes as leukopenic myelosis a form of aleukemic leukemia which is marked by progressive anemia, a hemorrhagic tendency and liability to necrotic angina. An acute, a subacute and a chronic form are encountered. On sternal puncture a preponderance of primitive myeloid cells, mostly myeloblasts, is observed, with occasional hyperplasia of the erythropoietic tissues. There may be terminal leukocytosis. The anemia may be of the orthochromic or the hyperchromic type, with reticulocytosis and erythroblastosis at times. Thrombopenia may indicate a bad prognosis.

Of 86 patients with leukemia (39 with myelogenous and 47 with lymphogenous leukemia) treated at the Johns Hopkins Hospital (1926 to 1938), Wintrobe and Hasenbush⁴³⁸ found that 61.5 per cent of the first group and 83 per cent of the second were men. The onset in 72 per cent of the former group occurred between the ages of 30 and 59 years, in 61.7 of the latter group it occurred between the ages of 50 and 69 years. Unexplained polymorphonuclear leukocytosis may be the initial abnormality in cases of myelogenous leukemia, while only one third of the patients with lymphogenous leukemia showed early unexplained leukocytosis. Patients of this type showed slight anemia more frequently than did the group with myelogenous leukemia. The interval from the initial symptom to the time that medical aid was sought was two to five years for patients with myelogenous leukemia and one and one-half to two and one-half years for those with lymphatic leukemia. Infection was more common in the latter type, and it did not produce symptoms of remission in either type. Solution of potassium arsenite U.S.P. was ineffective in cases of lymphogenous leukemia, and while it was of value in cases of the myelogenous type, it was less effective than roentgen therapy.

Leukemoid reactions of the myeloid type were studied by Heck and Hall¹³². These include pyogenic infections, subacute bacterial endocarditis, tuberculosis, hemolytic anemia, pernicious anemia, polycythaemia vera, chronic lymphatic leukemia, Hodgkin's disease, essential thrombopenia, erythroblastic anemia, acute loss of blood, severe anemia, granulocytopenia, metastases to bone marrow, multiple myeloma, osteosclerosis,

437 Scott, R. B. Leukopenic Myelosis, *Proc Roy Soc Med* **32** 1429, 1939.

438 Wintrobe, M. M., and Hasenbush, L. L. Chronic Leukemia. The Early Phase of Chronic Leukemia, the Results of Treatment and the Effects of Complicating Infections, a Study of Eighty-Six Adults, *Arch Int Med* **64** 701 (Oct.) 1939.

diabetic coma and certain chemical poisonings. In these conditions immature bone marrow cells may be noted in the blood stream at times. The authors state that in most of the cases studied differentiation from leukemia could be made on the basis of clinical observations. Leukocyte counts above 100,000 per cubic millimeter were observed rarely in conditions other than chronic forms of leukemia, while many leukemic patients had counts which fell within or below the normal range. Approximately 40 per cent of all patients with acute leukemia and 10 per cent of all patients with chronic leukemia seen at the Mayo Clinic from 1928 to 1933 inclusive had leukocyte counts below 10,000 cells per cubic millimeter.

The special aspects of leukemia in children are discussed by Edward,⁴³⁹ Booth and Rembolt⁴⁴⁰ and Jelke⁴⁴¹ (acute lymphatic leukemia in unioval twins).

Experimental Leukemia in Animals—The work of Kirschbaum and Strong⁴⁴² is significant in throwing some light on the nature of leukemia and the leukemic "soil" in susceptible subjects. In a group of mice (known as the F strain) inbred for twelve years (30 generations), enlarged spleens, lymph nodes or thymus glands were noted in over 200. Of the last 22 animals over 6 months of age which were killed or which died, 10 had either leukemia or mediastinal lymphosarcoma. In 17 cases of spontaneous leukemia and lymphosarcoma, both myelogenous and lymphatic leukemia, as well as leukemia of other types, developed. It was possible to transmit these to 295 mice of the F strain by subcutaneous or intraperitoneal inoculation of cells. Each type of inoculated cell bred true to type, suggesting proliferation of the introduced cells rather than transformation of reticuloendothelial or other mesenchymal cells. The neoplastic nature of the leukemic cells was evidenced by primary tumor formation followed by systemic leukemia, except after intraperitoneal injection of the cells, in which case the tumor phase was absent in some animals. Leukemic cells showed a wide degree of cytologic variation, and there appeared to be no specific cytomorphologic criteria for malignancy. Leukemic cells frequently had characteristics of normal young cells.

439 Edward, D. G. F. *Leukaemia in Children*, Clin J 68 100, 1939.

440 Booth, M., and Rembolt, R. R. *Leukemia in Childhood. Evaluation of Present Status of Problem with Particular Reference to Study of Cases Treated at University of Minnesota Hospitals from 1930 to 1938*, Journal-Lancet 59 216, 1939.

441 Jelke, H. *Acute Lymphatic Leukemia in Uni-Oval Twins. I. Etiology*, Acta pædiat 27 87, 1939.

442 Kirschbaum, A. and Strong, L. C. *Leukemia in the F Strain of Mice. Observations on Cytology, General Morphology and Transmission*, Am J Cancer 37 400, 1939.

MacDowell, Potter and Taylor⁴⁴³ found that leukemic cells became more virulent after a long series of transfers from one animal to another. However, mice naturally susceptible to these highly virulent cells could be rendered resistant to these cells by intraperitoneal injection of graduated, increasing doses of the virulent cells or by intraperitoneal injection of a saline suspension of liver cells of these immunized mice or of embryonic tissue or normal liver suspensions from a special strain of mice. The immunized hosts, however, were still susceptible to the development of spontaneous leukemia.

Barnes and Sisman⁴⁴⁴ studied myelogenous leukemia in mice, comparing it with nonmalignant extramedullary myelopoiesis. In the latter condition the abnormalities associated with malignant disease are absent, and all stages in the development of both white and red blood cells are present, contrasting with the predominance of immature myeloid cells in the presence of leukemia. Parenteral administration of suspensions of *B. coli* stimulates extramedullary hemopoiesis in rats. Exposure of mice with mammary tumors to small doses of roentgen rays did not produce myelogenous leukemia, and it failed to increase the extent of nonmalignant extramedullary myelopoiesis.

In mice, susceptibility plays an important part in the transmission of leukemia. In Schweitzer and Furth's⁴⁴⁵ experiments there was a dominance in the inheritance of susceptibility in hybrids between susceptible and nonsusceptible stocks. The duration of the illness and the anatomic characteristics of the leukemia were not modified by the genotype of the host. Lewis⁴⁴⁶ described a transplantable monocytoma in a mouse into which dibenzanthracene had been injected. Living cells were necessary to transmit the tumor, there being no evidence of a virus or of infectious organisms.

Furth⁴⁴⁷ studied a spontaneous mouse tumor composed of monocytes. The morphologic structure of the cells and the microscopic appearance of the lesions were similar to those of neoplasms formed by histiocytes in the human being. Malignant histiocytes were necessary

443 MacDowell, E. C., Potter, J. S., and Taylor, M. J. Influence of Transplantation upon Immunological Properties of Leukemic Cells, *Proc. Nat. Acad. Sci.* **25** 416, 1939.

444 Barnes, W. A., and Sisman, I. E. Myeloid Leukemia and Nonmalignant Extramedullary Myelopoiesis in Mice, *Am. J. Cancer* **37** 1, 1939.

445 Schweitzer, M. D., and Furth, J. Susceptibility to Transmitted Leukemia Occurring in Pure Bred and Hybrid Mice, *Am. J. Cancer* **37** 224, 1939.

446 Lewis, M. R. A Transmissible Monocytoma of the Mouse, *Am. J. Cancer* **36** 34, 1939.

447 Furth, J. A Neoplasm of Monocytes of Mice and Its Relation to Similar Neoplasms of Man, *J. Exper. Med.* **69** 13, 1939.

to transplant the tumor, and attempts to transmit the disease with cell-free material were unsuccessful

Kabat ⁴⁴⁸ observed a polysaccharide in tumors produced by a virus causing fowl sarcoma and leukosis. It was similar in its chemical properties and in its behavior toward a pneumococcus enzyme preparation to the substance isolated from vitreous humor, the umbilical cord, the synovial fluid and the mucoid hemolytic streptococcus

Stern and Kirschbaum ⁴⁴⁹ isolated by ultracentrifugation of saline extracts of leukotic fowl bone marrow a macromolecular material which contained the active virus. The substance contained about 9.5 per cent nitrogen, as well as thymonucleic acid, hemin, cytochrome oxidase and catalase, although these enzymes may have been present in associated substances

Marchal, Patuël, Guérin and Guérin ⁴⁵⁰ noted that there was no change or a slight increase in globulin in hens inoculated with leukemia. After immunization there was a 50 per cent increase in the serum globulin concentration above normal

Jármay ⁴⁵¹ found that, while tissue emulsions of mouse carcinoma and mouse and rat sarcoma were inactivated by small doses of roentgen rays, erythroleukotic and sarcomatous tissue from fowls resisted much larger doses, suggesting that the causative agent is apparently of the nature of an enzyme

Furth ⁴⁵² has published an excellent review of 96 articles on experimental leukemia in birds and mammals. Among the agents which have produced leukemia are roentgen rays, benzene, indol, methylcholanthracene, estrogens and benzopyrene. Storti and Brotto ⁴⁵³ found that the substance which produces fowl leukemia on injection localizes primarily in the bone marrow, where it acts on the erythroblastic tissue. Some of the substance is taken up in the liver and spleen. After injection, the substance disappears rapidly from the blood stream but reappears after

448 Kabat, E. A. A Polysaccharide in Tumors Due to a Virus of Leucosis and Sarcoma of Fowls, *J Biol Chem* **130** 143, 1939

449 Stern, K. G., and Kirschbaum, A. On the Nature of the Agent Causing Leucosis in Fowls, *Science* **89** 610, 1939

450 Marchal, S., Patuël, L., Guérin, M., and Guérin, P. Recherches sur la teneur en protides du serum de poules inoculées avec une leucémie ou avec des sarcomes, *Compt rend Soc de biol* **131** 213, 1939

451 Jármay, K. Ueber die Röntgenresistenz des Agens der übertragbaren Tiergeschwulsten und zur den Agenzien der übertragbaren Huhnersarkome, *Arch f wissensch u prakt Tierh* **74** 67-74, 1939

452 Furth, J. Experimental Leukemia, in A Symposium on the Blood and Blood-Forming Organs, Madison, Wis., University of Wisconsin Press, 1939, p 105

453 Storti, E., and Brotto, M. Ueber die Pathogenese der übertragbaren Hühnerleukämie, *Folia haemat* **63** 1, 1939

a period of three days Extramedullary leukemic foci are metastatic and are not the result of the action of the leukemic virus on local hemistioblasts The authors consider fowl leukemia to be neoplastic

Hester and Graham ⁴⁵⁴ have described lymphatic leukemia in a pig 3 months old There were splenomegaly, lymphadenopathy, 18,250 lymphocytes per cubic millimeter of blood and invasion of the organs by lymphocytes

LEUKEMIA CHEMICAL AND PATHOLOGIC PICTURE

Data as to the nature of myeloblasts, lymphoblasts and "acute splenic tumor cells" have been accumulated by Rich, Lewis and Wintrobe ⁴⁵⁵ By analyzing the motions of the cells in vitro with the motion picture technic it was found that the lymphoblast and the myeloblast have a different behavior and that the splenic tumor cell resembles the former In cases of leukemia the behavior of the cells is the same as that of the stem cell which is involved, whether this is a lymphoblast or a myeloblast Lymphoid activity with lymphadenopathy and splenomegaly characterized the response to injection of foreign protein, suggesting a possible relation of the lymphocyte to antibody formation

Hirschberg ⁴⁵⁶ studied phagocytosis, the sedimentation rate and the occurrence of bacteria in the blood in 20 cases of different types of leukemia She found that the phagocytic power of leukemic blood was decreased, only from 30 to 70 per cent of the mature neutrophils showing phagocytic tendencies as compared with 96 per cent in the controls In the leukemic cells the range was from 2.6 to 38.2 bacteria per cell (controls, 18) The blood of subjects with the chronic condition was relatively free from bacteria, and in those with the acute condition in whose cases positive bacteriologic observations were made the infection appeared to be superimposed on the leukemia In 10 of the patients the sedimentation rate was normal, in the others, slow or rapid

Forconi ⁴⁵⁷ advocates puncture of both the spleen and the bone marrow as a check on the accuracy of the diagnosis and as a means of determining the involvement of the organs in a leukemic process

⁴⁵⁴ Hester, H. R., and Graham, R. Lymphocytoma or Lymphoid Leucemia in a Pig, *Cornell Vet* **29** 334, 1939

⁴⁵⁵ Rich, A. R., Lewis, M. R., and Wintrobe, M. M. The Nature of the Acute Splenic Tumor Cell, as Revealed by Comparative Motion Picture Studies of Cells of the Spleen, Lymph Nodes, Bone Marrow and Leukemic Blood, *Tr. A. Am. Physicians* **54** 188, 1939

⁴⁵⁶ Hirschberg, N. Phagocytic Activity in Leukemia, *Am. J. M. Sc.* **197** 706, 1939

⁴⁵⁷ Forconi, A. Pour confirmer l'importance des ponctions de la rate et de la moelle osseuse dans les myeloses érythrémiqes sub- et aleucémiques, *Sang* **13** 380, 1939

Kempner⁴⁵⁸ studied the metabolism of leukemic lymphocytes in a Warburg apparatus. Myeloblasts and lymphoblasts have a purely oxidative metabolism, differing from the mature forms, and do not form lactic acid under aerobic conditions. Anaerobic glycolysis of myeloblastic blood was seven and six-tenths times that of normal blood, and the respiratory rate was forty-seven times greater. The respiratory quotient of myeloblasts measured in air is 0.75. Aerobic glycolysis in more mature leukocytes is a symptom of senility and dying. Both myeloblasts and lymphoblasts have the metabolism of normal cells and not of cancer cells.

Rin,⁴⁵⁹ in studying the metabolism of leukocytes in a Warburg apparatus, found the respiratory and glycolytic rate to be increased above normal in the presence of both chronic myelogenous and chronic lymphatic leukemia. The author concludes that the metabolic type is that of fetal cells rather than that of malignant tumor tissue. The metabolism of immature leukocytes was active, that of myeloblasts being greater than that of lymphoblasts. The author sees no supportive evidence for classifying leukemia with malignant tumors.

Kuzuya⁴⁶⁰ found that of the total protein content the residual nitrogen content of the blood plasma was similar in acute, subacute and chronic myelogenous leukemia. Either the values for fibrinogen and for total proteins of the blood plasma were low normal or the fibrinogen content was increased in amount while the plasma residual nitrogen was increased. Fibrinogen increased in amount after roentgen therapy administered over the spleen.

Buchmann⁴⁶¹ found that the iron content of the serum was normal or increased in the presence of chronic leukemia, but in the presence of myeloblastic leukemia the serum iron decreased when the body temperature became elevated. The blood of patients with myelogenous leukemia gave a microchemical "nucleal" reaction for thymonucleic acid.

Voit and Borgard⁴⁶² found this reaction to be direct without previous hydrolysis. Vogelensang²³³ found that the zinc content of the leukocytes is higher than that of the red blood cells in cases of leukemia. Normally about 90 per cent of the zinc is in the erythrocytes.

458 Kempner, W. Nature of Leukemic Blood Cells as Determined by Their Metabolism, *J Clin Investigation* **18** 291, 1939.

459 Rin, Mo-Sei. The Metabolism of Leukocytes in Leukemia, *Acta haemat japon* **2** 351, 1938.

460 Kuzuya, K. Partition of Blood-Plasma Protein and Residual Nitrogen, *Ztschr f klin Path u Hamatol* **6** 269, 1937.

461 Buchmann, P. Die Bewegung des Serumeisens bei Myeloblastenleukämien, *Klin Wchnschr* **18** 281, 1939.

462 Voit, K., and Borgard, P. Zur Nuclealreaktion des myeloischen Blutbilds, *Klin Wchnschr* **18** 754, 1939.

Stodtmeister and Buchmann⁴⁶³ consider that iron deficiency accounts for the anemia occurring in the course of leukemia. The iron content of the serum is independent of the number of erythrocytes or leukocytes. A fall in the level of serum iron accompanies progressive deterioration and is a sign of poor prognosis. An increase in serum iron accompanies a remission induced by roentgen therapy.

By the use of radioactivated phosphorus in the form of disodium hydrogen phosphate (Na_2HPO_4) the phosphorus metabolism in 2 cases of chronic myelogenous leukemia was studied by Tuttle, Scott and Lawrence⁴⁶⁴. While the turnover of phosphorus in the red blood cells is rapid, the white blood cells retain this substance for a long time. One patient had retained 80 per cent. As 26 per cent of the cells in 1 patient and 33 per cent of those in the other were immature, it was not possible to say whether the handling of phosphorus by the leukocytes was normal (Lawrence and Scott⁴⁶⁵).

De Lucia and Morelli⁴⁶⁶ found that in patients with leukemia all blood phosphorus fractions except the inorganic ones are increased. After administration of vitamin B_1 all are slightly decreased. The same is true of the erythroblastoses. With anemias the various blood phosphorus fractions show values lower than normal. There is no appreciable difference in pernicious anemia and secondary anemia, and vitamin B_1 causes no change. The authors conclude that these variations of the level of blood phosphorus are not due to parallel variations in the number of blood cells but are the result of a direct action of vitamin B_1 on the blood phosphorus group, which is affected by various factors, including the action of the reticuloendothelial system.

Hemmeler⁴⁵⁰ found high values for serum iron in cases of pernicious anemia (200 micrograms per hundred cubic centimeters), increased amounts are noted in cases of hemolytic anemia, hemochromatosis, catarrhal jaundice and leukemia (normal values for males, 100 to 130 micrograms, and for females 80 to 100 micrograms, per hundred cubic centimeters).

The phosphatase values of whole blood, serum and urine were found by Iwatsuru and Nanjo⁴⁶⁷ to be increased in the presence of chronic

463 Stodtmeister, R., and Buchmann, P. Die Bedeutung des Serumeisenspiegels für die Beurteilung Leukämiekranker, *Klin Wchnschr* **18**:1365, 1939.

464 Tuttle, L. W., Scott, K. G., and Lawrence, J. H. Phosphorus Metabolism in Leukemic Blood, *Proc Soc Exper Biol & Med* **41**: 20, 1939.

465 Lawrence, J. H., and Scott, K. G. Comparative Metabolism of Phosphorus in Normal and Lymphomatous Animals, *Proc Soc Exper Biol & Med* **40**: 694, 1939.

466 De Lucia, P., and Morelli, A. Azione della vitamina B_1 sul quadro del P ematico in alcune emopatie, *Haematologica* **20**: 281, 1939.

467 Iwatsuru, R., and Nanjo, K. Studien über Phosphatase. VIII. Ueber die Phosphatasenaktivität des Blutes, Serums und Harns bei chronischer myeloischer Leukämie, *Biochem Ztschr* **300**: 422, 1939.

myelogenous leukemia After roentgen therapy the phosphatase content of the serum and, later that of the urine increase, suggesting that the myeloid leukocytes are sources of phosphatase in the blood and that when they are destroyed the phosphatase is eliminated in the urine

Albers⁴⁶⁸ did not note any deviation from normal in the levels of serum phosphatase in 21 cases of leukemia, but the values rose after roentgen therapy Koster⁴⁶⁹ reports increased phosphatase in the feces in the presence of leukemia

Keilhack⁴⁵ found large amounts of globulin but less albumin than normal in the femur marrow of a patient with chronic myelogenous leukemia The level of prothrombin in the blood was found to be slightly reduced in cases of acute leukemia by Scanlon, Brinkhous, Warner, Smith and Flynn³⁰⁹

In cases of leukemia Kreuzwendedich von dem Borne⁴⁷⁰ found that the vitamin C content of the blood was greatly increased, but there was a possibility that some nonspecific reducing substance might have complicated the test In the presence of clinical evidence of vitamin C deficiency, administration of ascorbic acid is without effect

Spellberg and Keeton⁴⁷¹ found increased utilization of ascorbic acid in cases of leukemia

Pennetti³⁵ found that the oxalic acid content of the blood was increased in certain cases of leukemia, probably as a result of hepatic insufficiency

Graff⁴⁷² found that the ratio of cholesterol to noncholesterol fractions in the blood serum in cases of leukemia was very high, owing to the extremely low values for the noncholesterol fraction, although the cholesterol fraction itself was lower than normal

Gingold⁴⁷³ found that the value for blood histamine is normally about 0.1 gamma per cubic centimeter, but with chronic myelogenous leukemia the value may be one hundred times this amount The histamine content of the blood in cases of lymphatic leukemia is not elevated

468 Albers, D Die Serumphosphatase bei myeloischer und lymphatischer Leukämie, *Ztschr f d ges exper Med* **105** 155, 1939

469 Koster, L The Occurrence of Glycerophosphatase in the Feces, *Nederl tijdschr v geneesk* **82** 5856, 1939

470 Kreuzwendedich von dem Borne, G A Actual and So-Called Vitamin C Deficiency, *Acta med Scandinav* **99** 449, 1939

471 Spellberg, M A, and Keeton, R W Excretion of Ascorbic Acid in Relation to Saturation and Utilization, with Some Diagnostic Implications, *Arch Int Med* **63** 1095 (June) 1939

472 Graff, U Untersuchungen über das Unverseifbare des menschlichen Serums, *Biochem Ztschr* **298** 179, 1938

473 Gingold, N Un element nouveau dans le diagnostic différentiel de la leucémie myéloïque chronique, *Bull Acad de med de Roumanie* **8** 382, 1939

to this extent Increase in oxidized glutathione was noted in cases of myelogenous leukemia, especially of the severe forms, by Weil, Aschenazy and Caprin,²²⁷ but this substance was reduced or absent in cases of lymphatic leukemia and of erythroblastosis No parallelism was found between the glutathione content and the basal metabolic rate when correlated with the cholesterol content of the blood In cases of myelogenous leukemia the concentration of total glutathione was 36.3 to 57.1 mg, that of reduced glutathione 35.5 to 53 mg and that of oxidized glutathione 0.5 to 4.1 mg per hundred cubic centimeters In cases of lymphatic and monocytic leukemia the values were total and reduced glutathione, 13.7 to 54.7 mg, and oxidized glutathione, 0 to 6.3 mg, per hundred cubic centimeters In cases of erythroblastosis they were total and reduced glutathione, 27.4 to 43.3 mg per cent, oxidized glutathione, 0

Kandel and Le Roy⁴⁷⁴ found that the reduced glutathione content of the blood of normal persons was 33.28 ± 2.83 per cent and the total glutathione content 40.20 ± 2.58 per cent, in patients with pernicious anemia, 33.92 ± 1.5 per cent, in patients with erythroblastic anemia 22.9 and 29.8 per cent, and in patients with polycythaemia vera, 65.36 and 75.16 per cent No definite correlation between the type of the disease and the glutathione content was evident, but there is a crude relation to the number of formed elements in the blood

Schultz³⁰ found a high concentration of glutathione in the blood of a patient with myelogenous leukemia, and Malenkova⁴⁷⁵ reported a similar finding, but the ratio of oxidized to reduced glutathione was below normal The increased glutathione was found mostly in the leukocytes

Grunke and Koletzko⁴⁷⁶ found that while patients with renal disease, neoplasms and pulmonary inflammations secreted an increased amount of the substance (present in normal urine) which favors coagulation of "artificial" hemophilic blood, patients with disease of the liver, pernicious anemia, leukemia and agranulocytic angina secreted but little or none of the substance

Clinical Data—A type of acute leukemia in which there is non-symptomatic hypertrophy of the thymus is described by Pierret, Chris-

474 Kandel, E. V., and LeRoy, G. V. The Blood Glutathione in Hematologic Diseases, *J. Lab. & Clin. Med.* **24** 669, 1939

475 Malenkova, K. M. The Glutathione Content of the Blood in Leukemic Patients, *Klin. med.* **16** 1007, 1938

476 Grunke, W., and Koletzko, T. Studien über die Blutgerinnung mit besonderer Berücksichtigung der Hamophilie. Einfluss des Harnes auf die künstlich verzögerte (hamophile-artige) Gerinnung des Plasmas, *Ztschr. f. d. ges. exper. Med.* **105** 46, 1939

tiaens, and Popoff⁴⁷⁷ The tumor is usually sensitive to roentgen rays, and great care is necessary in the application of roentgen therapy The authors suggest a study of the thymus before treatment in cases of leukemia, as well as a thorough study of the blood in any other case in which thymic tumor is discovered

A patient with eosinophil leukemia was studied by Thomsen and Plum,⁴⁷⁸ who found "a peculiar cell in the bone marrow (40%)" This cell, interpreted as the parent cell of the abnormal eosinophils of the blood, had a small, compact, often vacuolated nucleus, with colorless or faintly blue-staining cytoplasm with fine blue-green or eosinophil plaques or granules at the periphery The disease terminated as myeloblast leukemia

The relation of trauma and leukemia is discussed by Olovson⁴⁷⁹ in reporting 2 cases (fracture, concussion) Of 67 similar cases in the literature, there were 40 of trauma to the splenic region and 8 of fracture of a bone Considering the number of traumatized persons, traumatic leukemia is rare

The subject is also treated by Yaguda and Rosenthal⁴⁸⁰

An instance of the appearance of myelogenous leukemia in a young woman whose mother had died of the same disease fifteen years previously is cited by Laub⁴⁸¹ The author postulates a hereditary rather than an incidental relation between the 2 cases

Decastello⁴⁸² describes 6 cases of lymphatic leukemia in two generations of the same family Except for 1 patient who showed symptoms in youth and in whom the disease was of fourteen years' duration, the incidence was between the ages of 40 and 50 years Decastello feels that heredity may be a factor in leukemia

Court⁴⁸³ describes 2 cases of monocytic leukemia in childhood and reviews the cases reported previously There is no clearcut clinical picture, and the diagnosis must be made from data obtained from the blood and the sternal marrow and by biopsy of material from the lymph nodes

477 Pierret, R, Christiaens, L, and Popoff L'hypertrophie du thymus au cours de la leucémie aigue de l'enfant (a propos de trois cas), *Arch de méd d enf* **42** 5, 1939

478 Thomsen, S, and Plum, P Eosinophilic Leukemia, *Ugeskr f læger* **101**: 90, 1939, *Acta med Scandinav* **101** 116, 1939

479 Olovson, T Trauma und Leukämie, *Acta chir Scandinav* **82** 63, 1939

480 Yaguda, A, and Rosenthal, N Relation of Trauma to Leukemia, *Am J Clin Path* **9** 311, 1939

481 Laub, R Ueber familiares Auftreten der Leukämie, *Schweiz med Wchnschr* **69** 71, 1939

482 Decastello, A Aspects of Familial Leukemia, *Med Klin* **35** 1255, 1939

483 Court, D Monocytic Leukemia in Childhood, *Arch Dis Childhood* **14**. 231, 1939

Unusual infiltration of the eyelids with lymphoid cells in a 65 year old man with aleukemic lymphatic leukemia was noted by Tooke⁴⁸⁴. The local lesion regressed with roentgen therapy (1,000 to both lids), but the systemic disease progressed.

A hemolytic leukemoid condition in a man 34 years of age with angina is described by Gingold and Comsa⁴⁸⁵. A syndrome of prostration, urinary incontinence, dyspnea, extreme pallor with an icteric tint, splenomegaly, severe anemia, marked leukocytosis (white blood cell count, 112,000 per cubic millimeter), hemoglobinuria, cylindruria and nitrogen retention appeared. The leukemoid reaction and hemolytic process may have been induced or aggravated by neoarsphenamine and quinine given intravenously and prontosil (now known as azosulfamide [N N R], disodium 4-sulfamidophenyl-2'-azo-4'-acetyl-amino-1'-hydroxynaphthalene-3',6' disulfonate) given orally. The nonelevation of the uric acid and histamine content of the blood differentiated this condition from leukemia.

A case of leukemia is presented by Gandellini⁴⁸⁶ in which a myeloid and a lymphatic leukemic picture coexisted from the onset. There was chronic evolution, and the disease did not respond to any form of treatment. The clinical and pathologic-anatomic pictures were considered typical of "mixed" leukemia.

A patient with congenital leukemia is described by Morrison, Samwick and Rubinstein⁴⁸⁷. The leukocyte count rose to 300,000 per cubic millimeter before death, the blood showing many atypical myeloblasts. Chloromatous tumors were present on the back and scalp, and small infiltrations were scattered over the body.

From a detailed study of a case, Bianchi⁴⁸⁸ concludes that the essential histologic characteristics of acute erythremic myelosis are hyperplasia of the cells of the reticuloendothelial system with an exclusively erythroblastogenetic evolution and hyperplastic alterations of the secondary hemopoietic organs. Histoerythroblastic foci were demonstrated in the kidney, the adrenals, the myocardium and the testicles. These observations are interpreted as confirming the opinion of Di Guilelmo

484 Tooke, F. T. Case of Aleukemic Lymphosis Involving Upper Lids with Pathologic Findings, *Tr Am Ophth Soc* **36** 368, 1938.

485 Gingold, N., and Comsa, G. Anémie hemolytique aigue grave avec tableau leucemoide, consecutive a une angine traitee par divers agents chimiques, considerations pathogeniques, *Sang* **13** 517, 1939.

486 Gandellini, A. Contributo allo studio delle leucemie miste, *Haematologica* **20** 83, 1939.

487 Morrison, M., Samwick, A. A., and Rubinstein, R. I. Congenital Leukemia with "Chloroma," *Am J Dis Child* **58** 332 (Aug.) 1939.

488 Bianchi, C. Contributo clinico et anatomo-pathologico allo studio della mielosi erithremica acuta (malattia di Di Guglielmo), *Haematologica* **20** 213, 1939.

that acute leukemia and acute erythremia are analogous diseases with a common histogenetic foundation

Wynn-Williams' ⁴⁸⁹ patient (a woman aged 32 years) had ulcerative tonsillitis, and the leukocyte count was 16,800 per cubic millimeter. Of these, 62 per cent were lymphocytes, and there was no reduction in the number of neutrophils. Later, immature cells appeared (premyelocytes[?]), and there was mild anemia. The blood returned to normal with recovery. Because of this fact the disease was interpreted as an unusual response to a virulent streptococcal infection, rather than leukemia.

In McDonald and Waugh's case,⁴⁹⁰ postmenopausal bleeding was caused by leukemic (lymphatic) infiltration of the endometrium.

Fillis ⁴⁹¹ describes the development of acute myelogenous leukemia in a 58 year old woman after trauma to the right kidney and nephrectomy for uncontrollable renal hemorrhage. Radium treatment of the uterus may have been one of the inciting factors.

In describing a case of diabetes mellitus and chronic lymphatic leukemia, Hart, Lisa and Riedel ⁴⁹² conclude that the relation was probably fortuitous. The glycolytic rate was not abnormal. While the three types of leukemia are represented in reported cases, the lymphatic form is most common.

Two cases of chronic monocytic leukemia in women with marked cutaneous involvement are described by Freeman and Koletsky ⁴⁹³. In both there were extensive discrete, nodular cutaneous lesions, which in 1 case became confluent and indurated, with a bullous, fungating surface. The lymph nodes in the first case showed but slight involvement, with diffuse infiltration of the bone marrow (nondestructive), spleen, adrenal glands, kidneys and pituitary. In the other case there was widespread bulky involvement of the lymph nodes with focal and nodular (destructive) lesions of the bone marrow and a normal liver and spleen but infiltration occurred in the nose, tonsils, thyroid, stomach,

489 Wynn-Williams, N. Ulcerative Tonsillitis with Blood Count Simulating Lymphoid Leukaemia, *Brit M J* **1** 1032, 1939.

490 McDonald, J. R., and Waugh, J. M. Chronic Lymphatic Leukemia with Infiltration into Endometrium. Report of a Case, *Proc Staff Meet, Mayo Clin* **14** 465, 1939.

491 Fillis, B. E. Severe Unilateral Hematuria in a Case of Acute Myelogenous Leukemia, *J Urol* **42** 57, 1939.

492 Hart, J. F., Lisa, J. R., and Riedel, P. A. Diabetes Mellitus Complicated with Lymphatic Leukemia. Report of Case with Autopsy, *J A M A* **113**: 1222 (Sept 23) 1939.

493 Freeman, H. E., and Koletsky, S. Cutaneous Lesions in Monocytic Leukemia. Report of Two Cases with Pathologic Study, *Arch Dermat & Syph* **40** 218 (Aug) 1939.

lungs and pancreas. This case, in which leukopenia was present, may fall into the type of "reticuloendotheliosis" or of reticulum cell sarcoma.

Grayzel and Lederer⁴⁹⁴ describe a case of leukemic myelosis (aleukemic myelogenous leukemia) in a 13 year old girl, in which metastatic calcification was observed at autopsy in the lungs, left atrium, adrenal glands, kidneys, thymus gland and some of the moderate-sized arteries.

Grier and Richter⁴⁹⁵ describe the details of pregnancy coexisting with leukemia and analyze from the literature 28 cases of chronic leukemia and 25 cases of acute leukemia complicated by pregnancy. With acute leukemia the maternal mortality was 100 per cent within five weeks after delivery. With chronic leukemia many mothers lived at least two and one-half months, with a mortality of 51.7 per cent. The fetal mortality was 68 per cent in cases of acute leukemia and 37.1 per cent in cases of chronic leukemia. None of the babies had leukemia. The authors conclude that pregnancy should be avoided when leukemia is known to be present. Interference with pregnancy does not help the mother, and in the presence of acute leukemia shortens her life. The babies thus delivered are either premature or nonviable. In all except 1 of the cases of chronic leukemia the condition was myelogenous.

Tschopp's⁴⁹⁶ case is a contribution to the effect of pregnancy on the course of leukemia. His patient went through one normal pregnancy without evident aggravation of the disease, but operative termination of a second pregnancy, which had been progressing uneventfully for four or five months, was followed by rapidly developing myeloblastic overgrowth (acute leukemia), with a fatal termination. As to the part played by the pregnancy, the operation or the previous roentgen therapy (the leukocyte count had fallen to 4,000 per cubic millimeter) there is room for speculation.

Treatment—The prognostic significance of the presence or absence of myeloblasts in the blood stream is emphasized by Israëls⁴⁹⁷. Their presence is not of serious import if they disappear from the peripheral blood after roentgen therapy, but if they increase in number the outlook is grave. The myeloblastic transformation of the marrow parallels that of the blood. Treatment is effective when the relative number of immature forms decreases and the anemia improves. Israëls takes the view that roentgen therapy may be postponed in the presence of

494 Grayzel, D. M., and Lederer, M. Metastatic Calcification. Report of Two Cases, *Arch Int Med* **64** 136 (July) 1939.

495 Grier, R. M., and Richter, H. A. Pregnancy with Leucemia. Case Report and Review of Literature, *Am J Obst & Gynec* **37** 412, 1939.

496 Tschopp, W. Beitrag zur Frage der akuten Myeloblastenleukämie (Leukämie und Gravidität), *Folia haemat* **61** 319, 1939.

497 Israëls, M. C. G. Treatment of Chronic Myeloid Leukaemia. Importance of Myeloblast, *Lancet* **1** 317, 1939.

anemia provided that the progress of the disease and the condition of the patient do not require immediate irradiation therapy

The so-called "spray method" of treating leukemia is favored by Harrison and Reeves⁴⁹⁸ over the method of local treatment. Of 47 patients with leukemia of different types, 84 per cent of those treated with the spray method were living, as compared to 22 per cent who had local treatment and 56 per cent for whom the two methods were combined. This would suggest that the "local" method of treatment shortened the patients' lives. The authors consider that there is less danger of aplastic anemia with the spray method than with other methods, but its use is contraindicated in cases of aleukemic leukemia. Confirming previous authors, they feel that the total life span of the patient is not prolonged but that there is an added period of usefulness. While only 47 per cent of the 47 patients gave a history of previous infection, the authors consider that these observations lend weight to the infection theory of causation of leukemia.

Andrus and Holman¹¹⁷ removed the spleen from a patient with some type of aleukemic leukemia. The patient lived for four months after the operation, without improvement.

The use of radioactivated phosphorus in the treatment of leukemia was tested by Lawrence, Scott and Tuttle⁴⁹⁹. The types of leukemia tested were lymphatic, monocytic and chronic and acute myelogenous. Radioactivated phosphorus in the form of sodium phosphate solution was given by mouth at irregular intervals of from one to nine days for prolonged periods. A fall in the number of leukocytes, occasionally preceded by a rise, was followed, however, by death. The changes in the tissues at autopsy were interpreted as not indicating untoward effects from administration of the material. The major portion of each dose of "labeled" phosphorus is absorbed during the first three days and is thereafter excreted in small amounts in both urine and feces, chiefly in the former. There is greater deposition of the activated phosphorus in bone marrow and bone than in other human tissues and, at least in leukemic mice, a relatively large amount in leukemic osseous and lymphomatous tissue (Lawrence and Scott⁴⁹⁵).

Brauner and Gottlieb⁵⁰⁰ found that in the presence of leukemia and other conditions small doses of roentgen rays accelerate maturation of the granulocytes, increasing the number of polymorphonuclear cells in the bone marrow. There is a progressive decrease in the per cent of

498 Harrison, E. K., and Reeves, R. J. Roentgen Treatment of Leukemia, with Report of Pregnancy in Case of Lymphatic Leukemia, *Radiology* **32** 284, 1939.

499 Lawrence, J. H., Scott, K. G., and Tuttle, L. W. Studies on Leukemia with Aid of Radioactive Phosphorus, *Internat. Clin.* **3** 33, 1939.

500 Brauner, R., and Gottlieb, F. Les modifications du myelogramme au cours de la roentgentherapie, *Sang* **13** 963, 1939.

cells in the immature stages, with an increase in the number of those in more mature stages. Large doses inhibit the growth of the marrow cells. The changes in bone marrow appear early, some effects being evident in eight minutes, with the maximum effect in twenty-four to forty-eight hours.

Bean, Vilter and Spies⁵⁰¹ found that ether-soluble pigments having the color of porphyrin in 25 per cent hydrochloric acid, similar in appearance to those found in the urine of pellagics, appeared in the urine of patients with myelogenous leukemia as well as in that of healthy persons twelve hours after roentgen irradiation. They disappeared in forty-eight hours. Nicotinic acid administered before irradiation prevented excretion of the abnormal pigments but did not decrease the coenzyme content of the blood. Otherwise the blood codehydrogenases I and II decreased 60 to 90 per cent within twelve hours. A possible relation to "roentgen sickness" is postulated.

Bernard⁵⁰² found that colchicine given by mouth was therapeutically ineffective in cases of acute leukemia, but when given into the sternal marrow of a 5 year old boy with acute aleukemic leukemia it increased the degree of maturation of the leukocytes. Thus the leukoblastic cells of the marrow were reduced from 100 per cent to 41 per cent. There was no general improvement in the red blood cell picture or in the clinical condition, and the fatal evolution of the disease did not appear to be influenced.

MULTIPLE MYELOMA

Groscurin⁵⁰³ has published a review of 58 articles on multiple myeloma. An analysis of 40 cases of multiple myeloma was made by Batts⁵⁰⁴. Of the patients, 63 per cent were men, there was a family history of some type of neoplastic growth in 31 per cent of the cases, the average age was 53 years (range 28 to 73), the incidence was 1 case in 7,464 admissions to the hospital, a history of trauma was absent in 70 per cent of cases. The clinical history was not typical. The lesions were invariably multiple. The skull, spine, ribs, pelvis, shoulder girdle, humerus and femur were involved in decreasing frequency. The author states that Bence-Jones protein may be absent from the urine and that its presence is not always pathognomonic of the disease. While many

501 Bean, W. B., Vilter, R. W., and Spies, T. D. The Effect of Roentgen-Ray on the Blood Codehydrogenases I and II, *Ann Int Med* **13** 783, 1939.

502 Bernard, J. Leucémie aigue. Essai de traitement par les injections inter-médullaires de colchicine. Modifications médullaires et sanguines, *Sang* **13** 434, 1939.

503 Groscurin, T. R. Le myélome multiple, *Sang* **13** 30-65, 1939.

504 Batts, M., Jr. Multiple Myeloma. Review of Forty Cases, *Arch Surg* **39** 807 (Nov) 1939.

types of blood picture were encountered, the most constant finding was iron deficiency anemia (severe in 23 per cent of cases) The leukocyte count varied from low to 15,500 per cubic millimeter Plasma cells were reported in the blood in only 3 cases Roentgen therapy relieves pain and prolongs life (For nontreated patients the average duration of life after admission to the hospital was six months, for treated patients, twenty-three months)

Jersild⁵⁰⁵ found that of 27 patients with anticomplementary serum, 13 definitely and 5 probably had myelomatosis The reaction was carried out after the serum had been heated to from 56 to 60 C The globulin is increased in amount, and the coagulation temperature of the serum is often low

In Ulrich's⁵⁰⁶ case the values for blood protein and blood calcium were high, with normal or high values for serum phosphorus Bence Jones protein was present in the urine

Tarr and Ferris⁵⁰⁷ report the twelfth and thirteenth cases in the literature in which multiple myeloma was accompanied by tumor-like deposits of amyloid in and about the joints The amyloid was not abundant in the usual sites and frequently had an atypical staining reaction Bence Jones substance was present in the urine The involvement of the joints and muscles by amyloid masses simulated rheumatoid arthritis

GAUCHER'S DISEASE, HAND-SCHULLER-CHRISTIAN DISEASE AND NIEMANN-PICK DISEASE

Schleussner and Schnee⁵⁰⁸ summarize the present data about Gaucher's disease and describe a case of this condition in a 28 year old man They conclude that in cases of well advanced involvement a persistent leukopenia, even in the presence of a high temperature and a fulminating infection, is a diagnostic feature not present with other splenomegalies

The cerebroside in the spleen of a patient with Gaucher's disease was found by McConnell, Forbes and Apperly⁵⁰⁹ to be kersin No phrenosin was present

505 Jersild, M Diagnosing Myelomatosis with Complement Fixation, *J A M A* **113** 1119 (Sept 16) 1939

506 Ulrich, H Multiple Myeloma, *Arch Int Med* **64** 994 (Nov) 1939

507 Tarr, L, and Ferris, H W Multiple Myeloma Associated with Nodular Deposits of Amyloid in the Muscles and Joints and with Bence-Jones Proteinuria, *Arch Int Med* **64** 820 (Oct) 1939

508 Schleussner, R C, and Schnee, C F Gaucher's Disease A Brief Review of the Disease with Report of a Case in a Male, *New York State J Med* **39** 1665, 1939

509 McConnell, J S, Forbes, J C, and Apperly, F L Chemical Studies of a Gaucher Spleen, *Am J M Sc* **197** 90, 1939

Dworacek and Pesta⁵¹⁰ were able to produce histologic changes in the spleen of an animal by intraperitoneal injection of kerasin. The serum kerasin was increased by this procedure.

A case of malignant Gaucher's disease is described by de Lange⁵¹¹. A child of the same parents had died of the same disease. The patient, an infant, aged 2½ months, showed neurologic symptoms (hypertonia, opisthotonos, convulsions, a positive Kernig sign) with splenomegaly, hepatomegaly, leukopenia, thrombopenia and fever. Death followed at the age of 5 months. Fifteen cases in 8 families have been reported.

In the diagnosis of Hand-Schuller-Christian disease Schuller⁵¹² notes that roentgen evidence of hyperostotic osseous changes corresponding to the healing stage of xanthomatous processes in bone may be of diagnostic value. The bones involved may include the skull, pelvis and ribs. There may be roentgen evidence of milary pulmonary nodules and visible changes in the skin and eyelids. The response to roentgen therapy is of importance in the diagnosis. Diseases which may cause a mistaken diagnosis are syphilis, tuberculosis, malignant disease, myeloma, osteitis fibrosa cystica, suppurative osteomyelitis, meningococcal spina traumatica and circumscribed osteoporosis of the skull as seen with incipient Paget's disease.

Chargaff⁵¹³ isolated large amounts of sphingomyelin from the spleen of a patient with Niemann-Pick disease and obtained sphingosine, lignoceric acid and a mixture of palmitic and stearic acids on hydrolysis. Monoaminophosphatides containing 70 per cent cephalin were identified.

Lane and Smith⁵¹⁴ report 4 cases of Hand-Schuller-Christian disease with observations at autopsy. The cutaneous manifestations are emphasized.

BONE MARROW

With the popularization of the sternal puncture technic, there have been many references to quantitative data which are, in some cases, misleading. When material is drawn from the sternal marrow, it is

510 Dworacek, E, and Pesta, H. Ueber einen spektralanalytischen Nachweis des Kerasins und experimentelle Cerebrosidspeicherung im Linne eines Morbus Gaucher, *Wien klin Wchnschr* **52** 332, 1939.

511 de Lange, C. Malignant Form of Gaucher's Disease, *Acta pædiat* **27** 34, 1939.

512 Schuller, A. Diagnosis of Schuller-Christian's Disease, *Brit J Radiol* **12** 225, 1939.

513 Chargaff, E. The Spleen in a Case of Niemann-Pick's Disease, *J Biol Chem* **130** 503-511, 1939.

514 Lane, C W, and Smith, M G. Cutaneous Manifestations of Chronic (Idiopathic) Lipoidosis (Hand-Schuller-Christian's Disease). Report of Four Cases Including Autopsy Observations, *Arch Dermat & Syph* **39** 617-644 (April) 1939.

mixed with circulating blood, and all elements of the marrow are not washed out in equal proportion Scott,⁵¹⁵ however, assumes that if only 0.1 cc of material is withdrawn, it is pure marrow and is representative of all the marrow that remains in the sternal marrow cavity. He then reports differential counts of the cells to the first decimal place. In his "normals," myeloblasts vary 400 per cent. He does not take into account the fact that peripheral blood is mixed with the marrow and therefore finds 64 to 139 per cent of lymphocytes in normal marrow. Monocytes vary 300 per cent, basophilic normoblasts 283 per cent and myelocytes 700 per cent in different persons. Scott considers that authors using terminology that is different from his "abuse" the terms. He does not like the term "hemohistiocytes or blasts," so he does not find these cells present, forgetting that with his technic these cells may not be washed out. He finds no megaloblasts in normal bone marrow because he calls them pronormoblasts. He finds the technic useful in the diagnosis of myeloma, kala-azar and carcinoma.

Cotti⁵¹⁶ summarizes the criteria for the analysis of sternal puncture material as the total cell count, the relation between leukocyte and erythrocyte formation (normal, 3:1) and the per cent and quantitative relations between the stages of maturation and the number of cells undergoing mitosis.

Gordon⁵¹⁷ made quantitative studies of the cells of bone marrow by diluting them with acetic acid or with sodium citrate solution, and differential counts were made from films drawn from serum suspension of the cells. A somewhat similar method has been described by Isaacs⁵¹⁸. In a normal person Gordon found the red blood cells to number 1,132,000 and the nucleated cells 468,000 per cubic millimeter of rib marrow. The red blood cell count was distinctly higher than this in cases of Addison's disease, stillbirth and some infections. There was an appreciable increase in the number of nucleated cells in infections, acute nephritis, Addison's disease and leukemia. The red blood cell count was lowest in cases of lymphatic leukemia and aplastic anemia, in 1 case of the latter it was 110,000 per cubic millimeter, with 28,000 nucleated cells. The bone marrow of the sternum, ribs and vertebra is essentially similar in man.

515 Scott, R. B. Sternal Puncture in the Diagnosis of Diseases of the Blood-Forming Organs, *Quart J Med* **8** 127-172, 1939.

516 Cotti, L. Kriterien zur anatomisch-funktionellen Beurteilung des Knochenmarks. Methodik und physiopathologische Anwendungen, *Folia haemat* **62** 369, 1939.

517 Gordon, A. S. Studies in Bone Marrow, *J Lab & Clin Med* **24** 352, 1939.

518 Isaacs, R. Bone Marrow in Anemia. Red Blood Cells, *Am J M Sc* **193**:181, 1937.

Stasney and Higgins ⁵¹⁹ observed a remarkable correlation in the percentage distribution of the various marrow elements in the flat bones of 14 persons after accidental death and suggested that data obtained from one region of the marrow will reveal trends in other portions of the marrow throughout the body. The myeloid-erythroid ratio is normally greater than 1 under physiologic conditions.

Kandel and LeRoy ⁵²⁰ point out that the great variation in the number and types of cells in normal marrow make it impossible to place great reliance on subtle changes in the constitution of material obtained by sternal puncture. In some cases such material does not give diagnostic data or is misleading in not expressing the true nature or extent of the disease. Clinical examination is often more valuable than inadequate data obtained by sternal puncture. Bone marrow in cases of pernicious anemia shows conversion from megaloblastic to normoblastic within twenty-four hours after liver therapy is given.

Williams ⁵²¹ studied stained sections of bone marrow from various parts of the body from 288 persons representing 23 controls and also patients with many clinical conditions. Of those with presumably normal marrow, 39 per cent showed small lymphoid collections of cells. These appeared in a wide variety of diseases, often when no infection or significant inflammatory disease was demonstrable. They were found more frequently in persons over 40 years of age than in younger adults. The author concludes that no pathologic significance can be attached to these observations and that lymphoid nodules are essentially normal, though variable, constituents of active red bone marrow of adults.

Carbon injected into the bone marrow of dogs and titanium dioxide injected into that of rabbits in the experiments of Huggins ⁵²² showed a symmetric distribution. In the red bone marrow pattern, centripetal regression, greater growth and retention at the rapidly growing metaphyses and formation of a central fatty cone in the long tubular bones were demonstrated. The foreign particles were held by the phagocytic cells of the marrow, showing the extent to which the marrow takes part in this process.

In cases of macrocytic anemia produced in rats by administration of sulfanilamide, Higgins and Machella ⁵²³ found an initial myeloid

519 Stasney, J., and Higgins, G. M. A Cytologic Study of the Marrow in the Flat Bones of Man, *Folia haemat* **61** 334, 1939.

520 Kandel, E. V., and LeRoy, G. V. Limitations of Biopsy of Sternal Marrow, *Arch Int Med* **64** 121 (July) 1939.

521 Williams, R. J. The Lymphoid Nodules of Human Bone Marrow, *Am J Path* **25** 377, 1939.

522 Huggins, C. A Quantitative Study of the Activity of the Reticuloendothelial Structures in Bone Marrow in Normal and Ischemic Limbs as Indicated by India Ink and Titanium Dioxide, *Anat Rec* **74** 231, 1939.

523 Higgins, G. M., and Machella, T. E. The Bone Marrow of Rats Made Anemic by Administration of Sulfanilamide, *Anat Rec* **75** 529, 1939.

stimulation on the fourth day, but on the sixth day the per cent of erythroid cells exceeded that of the myeloid group in the marrow, accompanying the development of anemia in the peripheral blood. The myeloid-erythroid ratio, normally greater than 1, was always less than 1 from the sixth day on. There was no apparent eosinophilic stimulation in the marrow.

Nordenson⁵²⁴ found two kinds of reticulum cells in human bone marrow. The first was a multipotent, primitive lymphoid reticulum cell, and the second, a phagocytic reticulum cell. Blood monocytes are derived from both types. The phagocytic reticulum cells stain intravitaly and belong to the reticuloendothelial system. It is possible that the two types are identical but manifest different characteristics.

Stern⁵²⁵ points out that besides the diagnostic value of studies of the bone marrow, the element of prognosis is important, as the normal, pathologic or aplastic nature of the marrow can be obtained.

In newborn children, Lichtenstein and Nordenson⁵²⁶ found that the bone marrow did not differ markedly from that of the adult in regard to myelopoiesis and erythropoiesis. The latter is normoblastic, the "erythropoietic quotient" is 19 per cent (adults, 19 to 25 per cent). The authors describe the bone marrow of immature infants as "hyperplastic and youthfully immature in character." More immature cells appeared in the peripheral blood of such children than in that of normal infants. The "erythropoietic quotient" (for the peripheral blood) was 35 per cent during the first week of life and 32 per cent during the third. The maximum, 45 per cent, was noted at the age of 3 months, dropping to 24 per cent after eleven to fourteen months (i.e., more erythropoietic tissue, as compared with granulopoietic tissue, than normal). The marrow of premature infants is thus characterized as hyperplastic but insufficient, giving the paradoxical blood picture of hypoplastic anemia with leukopenia.

The sternal bone marrow in children was studied by Vogel and Bassen⁵²⁷. They punctured the thin manubrial well and sucked out marrow tissue. Total counts of nucleated cells varied from 50,000 to 1,000,000 per cubic millimeter, with an average of 300,000 to 400,000 for normal children. The ratio of myeloid to erythroid cells was

524 Nordenson, N. G. Eine experimentelle Studie über die menschlichen Knochenmarkretikulumzellen sowie ein Beitrag zur Frage der Monozytengnese, *Acta med Scandinav* **100**:507, 1939.

525 Stern, L. D. Bone Marrow from Clinical Diagnostic Viewpoint, *J. Michigan M. Soc.* **38**:38, 1939.

526 Lichtenstein, A., and Nordenson, N. G. Studies on Bone Marrow in Premature Children, *Folia haemat.* **63**:155, 1939.

527 Vogel, P., and Bassen, F. A. Sternal Marrow in Children in Normal and Pathologic States, *Am. J. Dis. Child.* **57**:245 (Feb.) 1939.

approximately 3 1 The changes in the bone marrow in pathologic conditions are described Study of the bone marrow is of diagnostic value in cases of leukemia, infectious mononucleosis (elimination of leukemia), Gaucher's disease and Niemann-Pick disease In other conditions, study of the marrow is helpful in eliminating other disease processes in making the diagnosis (Excellent photomicrographs are presented)

In children, Veeneklaas⁵²⁸ found that the manubrium is the best site for sternal puncture Megaloblasts 16 to 18 microns in diameter, similar to those found in the marrow of patients with pernicious anemia, are normal constituents but are present in small percentages In children less than 3 years old megaloblasts, myeloblasts and "lymphoblasts" are more numerous than in older children The marrow in the presence of pneumonia is characterized by an increase in myelocytes and plasma cells, and in cases of celiac disease large neutrophils (16 to 18 microns in diameter) appear In the presence of aleukemic leukemia the leukemic cells in the marrow are of diagnostic importance even in the presence of a relatively normal peripheral blood picture

Sternal puncture may be of great diagnostic help in cases of malaria, especially when the organisms cannot be found in the blood, according to the report of Schretzenmayr and Lancaster⁵²⁹ When there is chronic malaria with splenomegaly and hepatic cirrhosis, a pernicious anemia-like blood picture may develop, justifying the use of liver extract Sternal punctures are of value for the aplastic anemia associated with chronic ankylostomiasis In cases of smallpox the authors found a myeloid reaction, with an increase in reticulum and plasma cells Among the organisms which can be found in the sternal marrow are Leishman-Donovan bodies of kala-azar, as well as filaria and spirochetes Sternal fluid may supplant blood transfusion when the latter is impracticable

A considerable number of data have been accumulated by Osgood and Bracher⁵³⁰ concerning the behavior of surviving marrow cells in vitro and their reaction to roentgen rays There is a latent period of at least four days before polymorphonuclear neutrophils die, even after such large doses as 2,000 r The theory that roentgen rays act only on cells in mitotic division appears improbable, as the number of cells affected at one time is far greater than the number undergoing mitotic division As the probable duration of mitosis in these cells is in the neighborhood of twenty-four to one hundred hours, radium, which is

528 Veeneklaas, G M H Sternal Puncture in Children, *Maandschr v kindergeneesk* 8 45 and 118, 1938

529 Schretzenmayr, A, and Lancaster, R L Sternal Puncture with Special Reference to Its Application in Tropical Diseases in South China, *J Trop Med & Hyg* 41 341, 1938

530 Osgood, E E, and Bracher, G J Culture of Human Marrow Studies of the Effects of Roentgen-Rays, *Ann Int Med* 13 563, 1939

applied for long periods, would be more likely to affect a "sensitive" stage than roentgen rays, which are applied for short periods. Some lymphocytes survive a dose of 2,000 r, while others disappear after a dose of 50 r. The authors observed no marked difference in the behavior of leukemic and nonleukemic cells. Osgood⁵³¹ found that cultures of marrow were helpful in evaluation of antibacterial therapeutic measures. In cell cultures inoculated with *Staphylococcus aureus* or alpha streptococci (*Streptococcus viridans*), neoarsphenamine in concentrations of 3 to 9 parts per million was far more effective than a 1:10,000 concentration of either sulfanilamide or sulfapyridine and did not damage the marrow cells significantly.

The influence of thyroid secretion on the bone marrow is noted in the marked myeloid metaplasia. Jones¹⁴⁶ finds that it resembles myelogenous leukemia. With recovery the marrow returns to normal. In cases of myxedema the marrow is markedly hypoplastic, improving with thyroid or thyroxine medication.

The bone marrow in cases of mycosis fungoides, as studied by Lapière and de Weerd, ⁵³² shows a histiocytoid reaction and inconstant eosinophilia. In the advanced stage of the disease there is an inhibition of the maturation of metamyelocytes into neutrophilic leukocytes, as well as a disturbance in the growth of the erythroblasts.

The myeloid tissue of the bone marrow in patients with gastric or duodenal ulcers was found by Bertolo and Ravetta⁵³³ to be rich in cellular elements. When there were mild hemorrhages, the changes varied little from the normal. With severe hemorrhages there was an erythroblastic reaction, basophilic in the majority of cases. With moderate but persistent hemorrhage, basophilic and acidophilic erythroblasts were observed with signs of karyokinetic stimulation.

In the diagnosis of aplastic anemia, splenic anemia, Banti's disease, leukemia, metastatic neoplasm, Hodgkin's disease and thrombopenic purpura, Hardgrove and Van Hecke⁵³⁴ find aspiration of the sternal marrow of value.

⁵³¹ Osgood, E. E. Effectiveness of Neoarsphenamine, Sulfanilamide, Sulfapyridine in Marrow Cultures with *Staphylococci* and *Alpha Streptococci*, *Proc Soc Exper Biol & Med* **42** 795, 1939, Marrow Cultures, in *A Symposium on the Blood and Blood-Forming Organs*, Madison, Wis., University of Wisconsin Press, 1939, p. 219, *The Culture of Human Marrow as an Aid in the Evaluation of Therapeutic Agents*, *J Lab & Clin Med* **24** 954, 1939.

⁵³² Lapière, S., and de Weerd, W. L'aspect de la moelle osseuse dans le mycosis fongique, *Sang* **13** 393, 1939.

⁵³³ Bertolo, A., and Ravetta, M. Il tessuto mieloide nelle ulcere gastriche e duodenali, *Haematologica* **20** 273, 1939.

⁵³⁴ Hardgrove, M., and Van Hecke, L. J. Sternal Marrow Aspiration, *Wisconsin M J* **38** 111, 1939.

In 2 cases of carcinoma with metastases to the bone marrow Buchem and Hendriksen⁵³⁵ concluded that the abnormalities in the blood depended on extramedullary hemopoiesis from either mechanical or toxic insufficiency of the bone marrow

Poli⁵³⁶ found that the plasma in the marrow has a higher protein content than that of the blood. The bone marrow is considered as a place of formation of plasma proteins

Something of the nature of the fluid removed by sternal puncture is shown in the chemical analyses of Benda, Franchel, Ducatel and Nicolas⁵³⁷. In 25 normal persons the sugar in the marrow was equal to that in the blood or slightly less. In diabetic patients the level of marrow sugar was higher than that of blood sugar, but in other patients with hyperglycemia there was a wide variation. In 4 patients with anemia the marrow sugar was slightly greater (in per cent) than the blood sugar. The marrow iron in normal persons was slightly lower in amount than the blood iron (Benda, Poirot, and Franchel⁵³⁸). In 3 patients with anemia the iron in the marrow was from 8.9 to 9.4 per cent less than that in the blood, whereas in others the amount was equal to or greater than that in the blood, not depending on the number of red blood cells. In a case of bronze diabetes the level of iron in the marrow was 4.82 per cent higher than that in the blood, but after two months' treatment with insulin and ascorbic acid it was 5.09 to 6.07 per cent lower than that of the blood

HEMATOLOGIC METHODS

Studies of the level of hemoglobin and other hematologic values for newborn children have been reported by Waugh and his associates⁵³⁹. Using the Evelyn photoelectric colorimeter, they found an average level of hemoglobin at birth of 15.6 Gm per hundred cubic centimeters, with a decline of 0.66 Gm during the first nine days. The average hematocrit value at birth was 51.3 per cent, with a fall of 5.4 per cent in the nine day period. During this time the mean corpuscular hemoglobin con-

535 Buchem, F. S. P., and Hendriksen, T. J. M. Le syndrome sanguin en cas de tumeurs métastatiques de la moelle osseuse et de leucanémie, *Acta med Scandinav* **102** 243, 1939

536 Poli, E. Ricerche sull'emoproteinogenesi midollare, *Sperimentale, Arch di biol* **93** 455, 1939

537 Benda, R., Franchel, F., Ducatel, J., and Nicolas, J. Premiers resultats d'une etude sur le chemisme du suc medullaire preleve par ponctions sternales. La glycomyélie, *Bull et mem Soc med d hôp de Paris* **54** 378, 1938

538 Benda, R., Poirot, G., and Franchel, F. Recherches sur le fer medullaire, *Bull et mem Soc med d hôp de Paris* **54** 386, 1938

539 Waugh, T. R., Merchant, F. T., and Maughan, G. B. Blood Studies on the Newborn. Determination of Hemoglobin, Volume of Packed Red Cells, Reticulocytes, and Fragility of the Erythrocytes over a Nine-Day Period, *Am J M Sc* **198** 646, 1939

centration increased from 30 to 32 per cent. At birth the resistance to hypotonic solution of sodium chloride is the same as in the adult, during the first four days of life it increases, and subsequently it returns to normal.

The hemoglobin content of human blood was determined by Myers and Eddy⁵⁴⁰ by the Newcomer acid hematin, the Hanzel iron and the Bing and Baker benzidine method. The average value for hemoglobin in men was found to be 15.8 Gm. and for women 13.0 Gm. per hundred cubic centimeters of blood. The authors concluded that calculation of hemoglobin from the iron content of the blood appears to be justifiable. A relation between hemoglobin concentration and body weight in men and rabbits was found by Spealman⁵⁴¹. In men the hemoglobin content of the blood varies directly with the body weight, whereas in rabbits the relation is inverse. Hematologic standards for old men were formulated by Miller⁵⁴². There were 160 subjects ranging in age from 60 to 104. The average erythrocyte count was 4,460,000 per cubic millimeter, with a range (including 95 per cent of the cases) between 3,500,000 and 5,500,000. The mean value for hemoglobin was 14.3 Gm. per hundred cubic centimeters, with a range of 12.0 to 17.5 Gm. The decrease in values associated with age was attributed to chronic low grade infections, nephrosclerosis and diminished cellularity of the bone marrow. Hypertension produced no demonstrable increase in the number of red cells. The leukocyte and differential counts apparently were not affected by advancing years. Standard normal values for erythrocytes, hemoglobin and packed cell volume throughout the last two trimesters of pregnancy were established by Bethell, Gardiner and MacKinnon¹⁹⁰. The values for leukocytes and the sedimentation rates of young and older children and adolescents were studied by Osgood and his associates⁵⁴³.

540 Myers, V. C., and Eddy, H. M. The Hemoglobin Content of Human Blood, *J. Lab. & Clin. Med.* **24**: 502, 1939.

541 Spealman, C. R. Body Weight and Hemoglobin Concentration, *Virginia M. Monthly* **66**: 591, 1939.

542 Miller, I. Normal Hematologic Standards in the Aged, *J. Lab. & Clin. Med.* **24**: 1172, 1939.

543 Osgood, E. E., Baker, R. L., Brownlee, I. E., Osgood, M. W., Ellis, D. M., and Cohen, W. Total, Differential and Absolute Leukocyte Counts and Sedimentation Rates of Healthy Children Four to Seven Years of Age, *Am. J. Dis. Child.* **58**: 61 (July) 1939, Total, Differential and Absolute Leukocyte Counts and Sedimentation Rates for Healthy Children Eight to Fourteen Years of Age, *ibid.* **58**: 282 (Aug.) 1939, Total, Differential and Absolute Leukocyte Counts and Sedimentation Rates of Healthy Adolescents Fifteen to Eighteen Years of Age, *J. Lab. & Clin. Med.* **24**: 905, 1939. Osgood, E. E., Brownlee, I. E., Osgood, M. W., and Cohen, W. Total Differential and Absolute Leukocyte Counts and Sedimentation Rates Determined for Healthy Persons Nineteen Years of Age and Over, *Arch. Int. Med.* **64**: 105 (July) 1939.

Experimental studies on the effects of asphyxia were carried out by dei Poli and Cappellato⁵⁴⁴ Dogs, rabbits and cats were used, and asphyxia was produced by inhalation of carbon dioxide or illuminating gas Rapid induction of asphyxia, within thirty to ninety seconds, caused no alteration in numbers of erythrocytes or platelets or in the coagulation time of the blood led to mild leukocytosis, which persisted for five to seven days When asphyxia was produced more gradually, over a period of four to five minutes, a considerable increase occurred in the number of red cells, platelets and white cells both in the peripheral and in the central blood The changes were prevented by removal of the spleen Asphyxia produced over periods of ten to sixty minutes caused the same degree of changes in erythrocytes and leukocytes that occurred after the four to five minute period, but the increase in platelets was proportional to the degree of anoxemia The increase in platelets was attributed both to contraction of the spleen and to new platelet formation, as evidenced by histologic examination of the hemopoietic organs The coagulation time and the retraction of the clot were uninfluenced by asphyxia

Delayed rates of platelet disintegration during menstruation and in persons with hemophilia were observed by Lee and Erickson⁵⁴⁵ These authors²⁶⁵ also studied the platelets in normal persons and in subjects with hemorrhagic conditions Olef's method of platelet enumeration was employed, and 400,000 to 600,000 per cubic millimeter were found in the blood of healthy men and nonmenstruating women During menstruation there occurred a moderate decrease in the number of platelets Intradermal injections of platelets caused a local reaction in normal persons, no reaction in hemophiliacs, a marked reaction in patients with idiopathic thrombopenic purpura, a negative result in persons with aplastic anemia and either a positive or a negative response in persons with various types of secondary purpura

Direct enumeration and morphologic differentiation of platelets has been performed by Vilarino and Pimentel,⁵⁴⁶ who used a solution containing an anticoagulant and a preservative The solution is made up of 10 cc of 3.8 per cent solution of sodium citrate, 10 cc of solution of formaldehyde and 80 cc of physiologic solution of sodium chloride Equal parts of this fluid and venous blood are well mixed immediately

544 dei Poli, G., and Cappellato, M. Sulle modificazioni prodotte dalla asfissia negli elementi morfologici e nel tempo di coagulazione del sangue, ricerche sperimentali, *Haematologica* **20** 505, 1939

545 Lee, P., and Erickson, B. M. Platelet Studies in Menstruation and Hemophilia. Total and Differential Counts, Disintegration Rates and Lipid Distributions, *Proc Soc Exper Biol & Med* **39** 264, 1938

546 Vilarino, and Vazquez Pimentel, J. Ueber Thrombocytenzahlungen, *Klin Wchnschr* **37** 1253, 1939

after withdrawal By this procedure the authors claim that change in the number and form of platelets can be prevented for as long as twenty-four hours, even at room temperature and without asepsis or paraffin coating of glassware

Recently the Westergren method of measuring erythrocyte sedimentation has enjoyed increased popularity Hambleton and Christianson⁵⁴⁷ found that this procedure, with a tube 200 mm long and an anticoagulant consisting of 15 to 20 per cent (by volume) of 3.8 per cent sodium citrate solution with a single reading at one hour gave results clinically more valuable than methods involving the use of heparin, correction for cell volume and graphic recording of results Lamb⁵⁴⁸ has emphasized the value of the sedimentation test to the general practitioner, and he considers correction for changes in red cell volume usually unnecessary He recommends the use of the Westergren tube and a dry anticoagulant, ammonium oxalate 12 mg and potassium oxalate 0.8 mg for each cubic centimeter of blood, with readings at one hour Studies in conjunction of the sedimentation rate and the non-filament ratio were made by Stiles⁵⁴⁹ in 292 cases of low grade chronic illness The nonfilamented neutrophil ratio was expressed in percentage of the total neutrophils The Westergren method was used without correction for anemia All patients with symptoms of low grade chronic disease showed an increase in the nonfilament ratio, with a mean value of 25.2 per cent as compared to a normal average ratio of 6 per cent More than 80 per cent of the patients exhibited an increase in the sedimentation rate, with an average fall of 15.9 mm in one hour, as contrasted with 3 mm and 5 mm, the normal limits for men and women, respectively A direct relation was established between the results of both tests and increases in the severity of the illness The nonfilament ratio appeared to reflect acute exacerbations, whereas the sedimentation rate was of greatest value in the diagnosis and follow-up of chronic illnesses

A five hour sedimentation test was devised by Cutbill,⁵⁵⁰ who used the Westergren tube The degree of fall in each of the successive hours is expressed by means of an index A new type of sedimentation tube

547 Hambleton, A., and Christianson, R. A. The Choice of Technique for the Sedimentation Test, *Am J M Sc* **198** 177, 1939

548 Lamb, F. H. The Blood Sedimentation Test, *J Iowa M Soc* **29** 589, 1939

549 Stiles, M. H. Sedimentation Rate and Non-Filament Ratio in Low Grade Chronic Illness. A Statistical Analysis of Two Hundred and Ninety-Two Cases, *Arch Int Med* **63** 664 (April) 1939

550 Cutbill, L. J. An Index of the Sedimentation Rate on a Mathematical Basis, *Ann Rheumat Dis* **1** 359, 1939

has been employed by Collins and his associates⁵⁵¹ Dry potassium oxalate, 2 mg per cubic centimeter of blood, is used as an anticoagulant, a 5 cc graduated conical centrifuge tube is filled with blood, and the fall in red cells is read in one hour Values are corrected to a packed cell volume of 42 per cent The correction formulas are as follows If the packed cell volume (P C V) is less than 42 per cent, add $1.5 \times (42 - \text{P C V})$ to the uncorrected reading, if P C V is greater than 42 per cent, subtract $1 \times (\text{P C V} - 42)$ from the uncorrected reading The authors conclude that this method is the most accurate and informative of several tested Brooks⁵⁵² described an instrument for measuring the sedimentation rate, which consists of a graduated pipet with a stopcock which may be attached directly to a needle used for venipuncture The pipet is rinsed with an anticoagulant solution before being filled with blood to the 100 mm mark It is then disconnected from the needle and set upright A photographic recording apparatus for the sedimentation rate has been devised by Nichols⁵⁵³

Day⁵⁵⁴ has pointed out that the reaction involved in the sedimentation of erythrocytes includes two incalculable phases (1) rouleau formation at the beginning of the process and (2) packing effect at its conclusion Consequently he advocates measuring only the maximum velocity of the fall rather than its total extent in a one hour period However, the phase of rouleau formation, which the author wishes to disregard, is probably of considerable clinical significance A recent review of the status of the sedimentation test has been published by Johnson⁵⁵⁵

A method for the construction of hematocrit tubes from capillary glass tubing of uniform bore is described by Miller⁵⁵⁶

Photoelectric optical methods for the study of blood coagulation have been reported by Lian and his associates,⁵⁵⁷ and by Nygaard⁵⁵⁸ The

551 Collins, D H , Gibson, H J , Race, J , and Salt, H B The Erythrocyte Sedimentation Test A Wide-Bore Tube Method Using Oxalated Blood and Permitting Correction of the Result to a Standard Red Cell Volume, *Ann Rheumat Dis* **1** 333, 1939

552 Brooks, C New Technic for Blood Sedimentation Test, *J M A Alabama* **9** 72, 1939

553 Nichols, R E A New Instrument for Automatically Recording the Erythrocyte Sedimentation Rate and the Volume Percentage of Cells and Plasma upon a Single Permanent Record, *J Lab & Clin Med* **24** 631, 1939

554 Day, G The Behavior of Sedimenting Blood, *Tubercle* **20** 364, 1939

555 Johnson, A S The Present Status of the Blood Sedimentation Rate, *New England J Med* **220** 823, 1939

556 Miller, A T, Jr A Simple and Accurate Hematocrit Tube, *J Lab & Clin Med* **24** 547, 1939

557 Lian, C , Frumusan, P , and Sassier Methode optique por l'etude de la coagulation sanguine Technique et resultats, *Sang* **13** 52, 1939

558 Nygaard, K K A New Apparatus for Photoelectric Recording of the Coagulability of Blood and Other Progressing Processes, *J Lab & Clin Med* **24** 517, 1939

latter distinguishes four phases during the coagulation process, which may be recorded graphically in terms of changes of optical density of the plasma (1) initial formation of fibrin, (2) period of gel formation, (3) rest period and (4) clot retraction period. Methods for the determination of the prothrombin content of the blood have been discussed elsewhere in this review.

The Weltmann serum coagulation reaction has been investigated by Levinson and Klein.⁵⁵⁹ The test is said to distinguish between exudative and fibrotic processes. The reaction does not parallel the sedimentation rate but, according to the authors, seems to reflect more accurately the actual pathologic anatomic changes. The test is said to be especially valuable in the study of tuberculosis and rheumatic fever and in distinguishing septic from nonseptic febrile conditions.

559 Levinson, S. A., and Klein, R. I. The Value of the Weltmann Serum Coagulation Reaction as a Laboratory Diagnostic Aid. Comparison with the Sedimentation Rate, *Ann Int Med* **12** 1948, 1939.

REVIEW OF LITERATURE ON THE PITUITARY BODY (1938 AND 1939)

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This review, as was the last one on this subject,¹ is written by and for clinicians. Those who desire a more comprehensive review are referred to the second edition of Van Dyke's book, "The Physiology and Pharmacology of the Pituitary Body"². Other reviews have been published in the current literature³.

We have attempted to list our references under different headings, but overlapping has occurred. There have been errors of omission and commission in selecting these references, and not all of them are of equal importance. It is hoped, however, that the review is sufficiently complete to inform the reader as to current developments and trends in this young and fast changing field of endocrinology.

ROLE OF THE PITUITARY BODY IN CARBOHYDRATE METABOLISM

It is exceedingly difficult to separate the discussion of the metabolism of any single food constituent from that of the metabolism of other food constituents. It is equally difficult to interpret any phase of metabolism in terms of any single gland. The relation of the pituitary body to the metabolism of carbohydrate foods is therefore complex.

From the Division of Medicine, the Mayo Clinic

1 Ryneerson, E H, and Hodgson, C H. Recent Advances in Knowledge of the Anterior Lobe of the Hypophysis, *Arch Int Med* **62** 160-176 (July) 1938

2 Van Dyke, H B. The Physiology and Pharmacology of the Pituitary Body, Chicago, University of Chicago Press, 1938, vol 2

3 Collip, J B. Results of Recent Studies on Anterior Pituitary Hormone, *Edinburgh M J* **45** 782-804 (Nov) 1938. Evans, H M. Endocrine Glands Gonads, Pituitary, and Adrenals, *Ann Rev Physiol* **1** 577-652, 1939. Jensen, H, and Tolksdorf, S. The Relation of the Anterior Pituitary to Sex and Metabolism, *Endocrinology* **25** 429-436 (Sept) 1939. Sexton, D L. Experiences with Pituitary Hormone Therapy, *Tr Am Therap Soc* **38** 89-95, 1938

A complete review of this subject was written by Jane Russell⁴ Because of its importance, we wish to quote her summary in its entirety

The complex relationship of the anterior pituitary to carbohydrate metabolism has only just begun to be explored. Some facts have been established definitely, and the discussions in this paper concerning the most important of these may be summarized as follows

1 Hypophysectomized animals are remarkably hypersensitive to insulin and may show diminished responses to epinephrine. Although several theories have been advanced to explain these abnormalities, none is sufficiently supported by present evidence to be accepted as final.

2 The removal of the hypophysis alters markedly the response of the animal to pancreatectomy, apparently ameliorating the effects of this operation. Possible mechanisms for this action have been discussed.

3 Anterior lobe extracts may affect the carbohydrate metabolism of normal, depancreatized or depancreatized-hypophysectomized animals in a manner which is outwardly "contra-insular" or "diabetogenic." This action cannot be considered simply in this light, however, for not all of the effects are similar to those of pancreatectomy, and the mechanism of their action is unknown.

Other types of action of anterior lobe extracts on the carbohydrate metabolism of normal animals are not at present well enough established to be given a definite place in anterior pituitary physiology.

4 Hypophysectomized animals when in good condition and well fed exhibit no marked abnormalities in their carbohydrate metabolism except those noted above, but they suffer an impairment in the normal mechanism by which blood sugar levels are maintained and, apparently, by which the tissue carbohydrate reserves are preserved, in conditions in which the carbohydrate supply is interrupted (as in fasting, phlorhizin poisoning, etc.).

In the rat, the abnormal rate of depletion of carbohydrate reserves during fasting is accompanied by an apparent increase in the rate of carbohydrate oxidation. Both of these effects can be prevented by anterior lobe therapy.

Two principal theories have been advanced in explanation of these and related findings—one, that the anterior lobe controls gluconeogenesis from endogenous protein, if not from fat, administration of its extract causing an increase in available glucose and its removal curtailing the supply, the other theory, that the anterior lobe influences carbohydrate oxidation itself, its presence preventing carbohydrate loss below certain levels and its absence characterized by lack of restraint on carbohydrate oxidation under conditions when such would ordinarily occur. Although this reviewer inclines to the latter explanation, at present it is not possible to make a final decision as to the validity or completeness of either of these theories.

Many observers were deeply impressed with the close and important relation between the anterior lobe of the pituitary body and carbohydrate metabolism⁵ but said they did not believe that a pituitary hormone would produce permanent diabetes mellitus. The first evidence of such

4 Russell, J. A. The Relation of the Anterior Pituitary to Carbohydrate Metabolism, *Physiol. Rev.* **18** 1-27 (Jan) 1938.

5 Long, C. N. H. The Relation of Anterior Pituitary to Carbohydrate Metabolism, *A Research Nerv. & Ment. Dis. Proc.* (1936) **17** 276-286 1938.

an effect was reported by Young⁶ in two papers published in March 1938. He used a crude anterior pituitary extract obtained from oxen on mice, rats, guinea pigs, rabbits, cats and dogs. The mice, rats and guinea pigs appeared to be almost totally insensitive to the diabetogenic action of this extract, in the case of rabbits and cats, glycosuria and ketonuria followed the daily injection of crude extract in 25 to 50 per cent of cases, but with dogs he had only 1 failure in 25 experiments. Young reported that in the dog glycosuria, hyperglycemia and ketonuria appeared after three or four injections and then disappeared and reappeared when an increased dose was given. When sufficient amounts were administered, the diabetic condition was found to continue indefinitely after cessation of the injections. This extract caused no immediate marked increase in the blood sugar, but required three or four daily injections.

Young was wise in emphasizing that the principle concerned should be called "diabetogenic factor" (rather than a "diabetogenic hormone"), and he suggested that this name be reserved for the substance or substances in an anterior pituitary extract which possess diabetogenic activity and which have little or no effect on blood sugar values within a few hours after the injection. The diabetogenic effect, he said, is contained in neither prolactin⁷ nor the glycotropic (anti-insulin) factor⁸ with which it is closely associated, but is a distinct substance, since the administration of prolactin or of the glycotropic (anti-insulin) factor does not induce a diabetic condition but produces, rather, transient glycosuria, unaccompanied by polyuria and ketonuria. This "hormone" has been further studied by Himsworth and Scott.⁹

This important work was repeated by Campbell and Best,¹⁰ who injected an extract into a normal dog for seventeen days, with the production of a gradually increasing diabetogenic response. On the

6 Young, F. G. The Diabetogenic Action of Crude Anterior Pituitary Extracts, *Biochem J* **32** 513-523 (March) 1938, Studies on the Fractionation of Diabetogenic Extracts of Anterior Pituitary Gland, *ibid* **32** 524-533 (March) 1938.

7 Anderson, C. M. Pituitary Gland and Carbohydrate Metabolism. Influence of Prolactin on Carbohydrate Metabolism, *M. J. Australia* **1** 701-704 (April 16) 1938.

8 Newton, W. H., and Young, F. G. The Influence of the Glycotropic (Anti-Insulin) Factor of the Anterior Hypophysis on the Insulin Sensitivity of the Hypophysectomized Rabbit, *J. Physiol.* **94** 40-46 (Oct. 14) 1938.

9 Himsworth, H. P., and Scott, D. B. M. The Action of Young's Glycotropic Factor of the Anterior Pituitary Gland, *J. Physiol.* **92** 183-207 (March 14) 1938.

10 Campbell, J., and Best, C. H. Production of Diabetes in Dogs by Anterior-Pituitary Extracts, *Lancet* **1** 1444-1445 (June 25) 1938.

seventeenth day the dog excreted 126 Gm of sugar, and after the injections of the extract were stopped excretion of dextrose continued in even greater quantities than before. It is interesting to note that the diabetes responded promptly to treatment with insulin. On the fifty-eighth day total pancreatectomy was performed and produced but slight effect on the requirement of insulin. The dog was later killed, and a section of the pancreas showed that an extreme degree of hydropic degeneration of the islet cells was present, with particularly extensive changes in the beta cells. An assay of the pancreas revealed a marked decrease in its content of insulin.

Dohan and Lukens¹¹ and Loubatières¹² also have corroborated the aforementioned finding. An effort has been made by Bergman and Turner¹³ to assay the diabetogenic hormone, but it is doubtful whether they were using the same hormone, since their test was dependent on a prompt response rather than on the more delayed and more permanent response reported by the other workers.

It is, of course, impossible to know how much of the effect of this and similar hormones is referable to direct action on the pancreas. Santo¹⁴ was not able to demonstrate any pancreatropic effect by means of histologic study of the pancreas of animals into which the pancreatropic hormone had been injected. However, the hormone may not have been effective, since Richardson and Young¹⁵ reported definite changes as occurring in the islet cells after the injection of a pancreatropic extract. Their method of study was unique in that they projected microscopic fields on sheets of cartridge paper. They then "cut out" different regions and weighed the islet and acinar regions separately. In this study they again found the peculiar differences which occur in species, for they observed a far different islet-acinar ratio in the Wistar strain of rats than in another strain. The extract which increased the islet-acinar ratio had little or no effect on the blood sugar of the rats studied.

11 Dohan, F. C., and Lukens, F. D. W. Persistent Diabetes Following the Injection of Anterior Pituitary Extract, *Am J Physiol* **125** 188-195 (Jan.) 1939.

12 Loubatières, A. Recherches sur le diabète sucré permanent consécutif aux injections d'extrait de lobe antérieur d'hypophyse chez le chien normal, *Compt rend Acad d sc* **208** 1933-1935 (June 12) 1939.

13 Bergman, A. J., and Turner, C. W. The Biological Assay of the Carbohydrate Metabolism Hormone of the Anterior Pituitary, *J Biol Chem* **123** 471-477 (April) 1938.

14 Santo, E. Die Beeinflussung der Langerhansschen Inseln durch das sog pankreatrope Hormon der Hypophyse, *Ztschr f d ges exper Med* **102** 390-406, 1938.

15 Richardson, K. C., and Young, F. G. The "Pancreatropic" Action of Anterior Pituitary Extracts, *J Physiol* **91** 352-364 (Dec 14) 1937.

In a second paper Richardson and Young¹⁶ reported on a study of the pancreas of dogs which had been rendered diabetic for at least ten months after the injections had been stopped, they observed marked changes in the islet cells, particularly hydropic degeneration and depletion of the cytoplasmic granules in the beta cells. There was some proliferation of the islet cells, a change which they said may precede exhaustive or degenerative processes that accompany the onset of permanent diabetes. They compared their results with those reported by Allan (1922), who found that, according to observations on his animals, the onset of diabetes is accompanied by functional exhaustion of the beta cells, then cytoplasmic granules are lost and the beta cells hypertrophy, next, vacuolation and disappearance of the cells occur after degeneration of nuclei.

The important relation of the adrenal cortex to carbohydrate metabolism is receiving much attention. Russell¹⁷ expressed the belief that there is a complementary and synergistic relation between the metabolic activities of the adrenal cortical hormone and those of the anterior pituitary hormones. Corey and Britton¹⁸ have restated their concepts, emphasizing the intimate relation between the pituitary and adrenal glands in carbohydrate metabolism. They concluded that the inability of hypophysectomized animals to maintain normal values for carbohydrates for short periods is explainable on the basis of adrenocortical deficiency, and they noted that the administration of adrenal cortical extract has been shown to be effective in maintaining normal and super-normal values for blood sugar and liver glycogen in hypophysectomized rats. Glycogen in the muscle likewise may be kept at approximately normal values. This extract will also restore the values for blood sugar and liver glycogen to normal levels in hypophysectomized rats which have been subjected to a twelve hour fast before the beginning of injections.

Bennett¹⁹ reviewed the evidence supporting the concept that the pituitary body directly influences the maintenance of fasting carbohydrate values in the rat rather than that this maintenance is achieved through the mediation of the adrenal gland. Hypophysectomized rats

16 Richardson, K. C., and Young, F. G. Histology of Diabetes Induced in Dogs by Injection of Anterior-Pituitary Extracts, *Lancet* **1** 1098-1101 (May 14) 1938

17 Russell, J. A. Effects of Anterior Pituitary and Adrenal Cortical Extracts on Metabolism of Adrenalectomized Rats Fed Glucose, *Proc Soc Exper Biol & Med* **41** 626-628 (June) 1939

18 Corey, E. L., and Britton, S. W. Hypophyseal and Adrenal Interrelationships and Carbohydrate Metabolism, *Am J Physiol* **126** 148-154 (May) 1939

19 Bennett, L. L. The Interrelation of Pituitary and Adrenal in the Control of Carbohydrate Levels in the Rat, *Endocrinology* **22** 193-196 (Feb) 1938

immediately after operation become unable to maintain fasting values for glycogen in the muscle, whereas this defect does not develop in adrenalectomized rats for several hours after operation. The fasting value for glycogen in the muscle of adrenalectomized rats is maintained within normal limits by treatment with adrenal cortical extract and salt, this treatment is without effect on hypophysectomized rats. Crude anterior pituitary extracts maintain the fasting glycogen value of hypophysectomized rats in the absence of both adrenal glands. Bennett stated the opinion that this factor, acting independently of the adrenal glands, has not been identified with any of the known hormones of the anterior lobe of the pituitary body.

Lukens and Dohan²⁰ found adrenal cortical extract capable of compensating to a considerable extent for the diabetes of adrenalectomized and depancreatized animals. Long and Katzin²¹ were able, by using an adrenal cortical extract (or Kendall's crystalline compound), to prevent the depletion of carbohydrate stores in fasting, hypophysectomized rats, and they succeeded in restoring the values for blood sugar, liver and muscle glycogen, even though these values first had been lowered by fasting. Long and Katzin did not attempt to define the mechanism of this effect, but suggested as its basis either a decreased utilization of carbohydrate or an increased production of dextrose from noncarbohydrate sources. Reiss and his associates²² treated hypophysectomized rats with corticotropic hormone and found that the therapy increased the ability of the animals to store sugar and fat.

Soskin and his co-workers²³ studied the relation of thyroxin to carbohydrate disturbances following hypophysectomy and found that administration of thyroxin would maintain a normal value for blood sugar through long periods of fasting. Thyroxin did not diminish sensitivity to insulin in the dogs in this series. This relation of sensitivity to insulin has been studied by Brobeck and associates,²⁴ who found that responses

20 Lukens, F. D. W., and Dohan, F. C. Further Observations on the Relation of the Adrenal Cortex to Experimental Diabetes, *Endocrinology* **22** 51-58 (Jan) 1938.

21 Long, C. N. H., and Katzin, B. Effect of Adrenal Cortical Hormone on Carbohydrate Stores of Fasted Hypophysectomized Rats, *Proc. Soc. Exper. Biol. & Med.* **38** 516-518 (May) 1938.

22 Reiss, M., Kusakabe, S., and Budlowsky, J. Zur Beziehung zwischen Hypophysenvorderlappen und Kohlehydratstoffwechsel, *Ztschr. f. d. ges. exper. Med.* **104** 55-70, 1938.

23 Soskin, S., Levine, R., and Heller, R. E. Rôle of the Thyroid in the Carbohydrate Disturbance Which Follows Hypophysectomy, *Am. J. Physiol.* **125** 220-226 (Feb) 1939.

24 Brobeck, J. R., Magoun, H. W., and Ranson, S. W. Insulin Sensitivity of Monkeys After Section of the Hypophyseal Stalk, *Proc. Soc. Exper. Biol. & Med.* **42** 622-624 (Nov) 1939.

to insulin may be entirely normal when only a half of the anterior lobe of the pituitary body is left intact. The presence of infundibular connections between the hypophysis and the pars distalis, however, is not essential for maintenance of normal sensitivity to insulin in the monkey and is probably not essential for maintenance of normal carbohydrate metabolism.

The important relation of the liver to carbohydrate metabolism has been studied by many investigators. Franseen, Brues and Richards²⁵ studied the effect of hypophysectomy on the restoration of the liver following partial hepatectomy in rats and found that restoration took place at a somewhat lower rate than in normal rats maintained on an optimal diet but at a more rapid rate than in fasting rats.

Soskin and his associates²⁶ found that hypophysectomized dogs utilized carbohydrate only about half as effectively as normal dogs. They concluded that the effects of hypophysectomy cannot be referable to an increased rate of utilization of sugar, since that rate is actually diminished. They wrote that hypoglycemia and other evidences of carbohydrate disturbance must be attributed to a proportionately greater decrease in the rate of new formation of sugar by the liver. Russell²⁷ has continued her studies in this field and has reported on a factor of the anterior lobe of the pituitary body which maintains glycogen in the muscles in fasting hypophysectomized rats, a factor which she said is not associated with the effect of many of the established hormones of the anterior lobe of the pituitary body. In a later article, Russell²⁸ concluded that the anterior lobe of the pituitary body is concerned not only with the preservation of carbohydrate values during the period of fast but also with the disposition of carbohydrate when the animal is fed. In the hypophysectomized rat the proportion of absorbed dextrose oxidized and the proportion of total calories obtained from carbohydrate sources were both much higher than in normal animals. Injection of an extract of the anterior lobe of the pituitary body into hypophysectomized and into normal rats caused an immediate decrease in the apparent rate of oxidation after feeding with carbohydrates.

25 Franseen, C. C., Brues, A. M., and Richards, R. L. The Effect of Hypophysectomy on the Restoration of the Liver Following Partial Hepatectomy in Rats, *Endocrinology* **23** 292-301 (Sept.) 1938.

26 Soskin, S., Levine, R., and Heller, R. E. Carbohydrate Utilization in the Hypophysectomized Dog, *Proc. Soc. Exper. Biol. & Med.* **38** 6-8 (Feb.) 1938.
Soskin, S., Levine, R., and Lehmann, W. Influence of the Hypophysis on Carbohydrate Metabolism, *Am. J. Physiol.* **127** 463-469 (Oct.) 1939.

27 Russell, J. A. The Anterior Pituitary Factor Which Maintains Muscle Glycogen in Fasted Hypophysectomized Rats, *Endocrinology* **22** 80-85 (Jan.) 1938.

28 Russell, J. A. The Effects of Hypophysectomy and of Anterior Pituitary Extracts on the Disposition of Fed Carbohydrate in Rats, *Am. J. Physiol.* **121** 755-764 (March) 1938.

Anderson,²⁹ Marks and Young³⁰ and Young³¹ also discussed the separate identity of this principle

Efforts to determine whether diabetogenic hormones are excreted in the urine continue. Clay and Lawson³² found that in the urine of 19 of 22 pancreatectomized dogs, a substance consistently appeared which had significant power to raise the values for sugar in the blood. Using rabbits as test animals, Clay and Lawson confirmed the presence in the urine of human beings with diabetes of a blood sugar-raising principle which is not found in the urine of normal persons. Administration of insulin and raw pancreas tissue did not cause disappearance of this principle from the urine of the depancreatized dogs. If, however, the dogs had been previously hypophysectomized, pancreatectomy did not cause the appearance of this substance in the urine. Hypophysectomy caused the principle to disappear from the urine of depancreatized dogs. Bjerling³³ studied the urine of healthy, of diabetic and of pregnant non-diabetic patients. He found in the urine obtained from healthy subjects, small quantities of a factor which had the power of elevating the values for blood sugar, in the urine obtained from some of the diabetic patients, an absolute increase of this principle, and in that of pregnant nondiabetic patients, large quantities of this principle. The urine of some of the diabetic patients did not contain an excessive amount of the principle. Lucke and his associates³⁴ studied the excretion of the contra-insular hormone and observed that the cerebrospinal fluid obtained from animals which were rendered markedly hypoglycemic had a hyperglycemic effect when injected into normal animals.

Clinical Aspects—Friedman³⁵ reported 2 cases in which the patients had hyperinsulinism and were found to have both the typical adenomas

29 Anderson, C. M. Anterior Pituitary Gland and Carbohydrate Metabolism, *M. J. Australia* **1** 11-19 (Jan. 1) 1938.

30 Marks, H. P., and Young, F. G. The Influence of Anterior Pituitary Extracts Injected Either With or Without Insulin, on the Glycogen Contained in the Livers of Fasting Young Rabbits, *J. Physiol.* **93** 61-73 (June 14) 1938.

31 Young, F. G. The Identity and Mechanism of Action of Glycotropic (Anti-Insulin) Substance of the Anterior Pituitary Gland, *Biochem. J.* **32** 1521-1539 (Sept.) 1938.

32 Clay, H. L., and Lawson, H. Relationship of Hyperglycemic Principle in Diabetic Urine to Pancreas and Hypophysis, *Am. J. Physiol.* **125** 566-570 (March) 1939.

33 Bjerling, T. Investigation of the Diabetogenous Hormone in Urine. Preliminary Report, *Acta med. Scandinav.* **94** 483-496, 1938.

34 Lucke, H., and Werner, R. Untersuchungen über die Ausscheidungsbedingungen des kontra-insularen Hormons aus dem Hypophysenvorderlappen, *Ztschr. f. d. ges. exper. Med.* **102** 242-247, 1938. Lucke, H., and Koch, A. Die reaktive Ausscheidung des kontra-insularen Vorderlappenhormons bei der Phlorrhizinglykosurie, *ibid.* **103** 270-273, 1938.

35 Friedman, N. B. Chronic Hypoglycemia. Report of Two Cases with Islet Adenoma and Changes in the Hypophysis, *Arch. Path.* **27** 994-1010 (June) 1939.

of the islets of Langerhans and changes in the basophilic and eosinophilic cells of the pituitary body

Shepardson and Shapiro³⁶ reviewed the subject of diabetes among bearded women and found only 17 clearcut cases of the condition, to which they added another case. Because of the rarity of true diabetes in the presence of disturbances of the adrenal cortex, they suggested that in those patients afflicted by the Achard-Thiers syndrome the precursor of diabetes must be present.

Bartelheimer³⁷ suggested the possibility that two types of diabetes might exist: one associated with underfunction of the islands of Langerhans and the other caused by hyperfunction of the anterior lobe of the pituitary body and the adrenal cortex.

Lassen and Hanson³⁸ injected an alkaline extract of the pituitary body into 3 patients with diabetes and obtained a diabetogenic effect.

Elmer and associates³⁹ found no evidence of a pancreatropic "blood sugar-decreasing" hormone and said that the anterior lobe of the pituitary body secreted only a blood sugar-raising substance, which they found in the blood of patients suffering from acromegaly.

Gessler and associates⁴⁰ studied the effect of injection of estrogenic substances on the blood sugar of female diabetic patients after the menopause. Among a small series of patients, they found a significant decrease in the value for fasting blood sugar in 2 patients in whom the onset of diabetes mellitus coincided with that of the menopause and also a decrease in this value in a patient in whom the menopause preceded the onset of diabetes mellitus. In 2 other patients no effect resulted from the injections of this estrogenic substance. Gessler and associates said that the beneficial effect was referable to inhibition of the pituitary diabetogenic factor by the estrogen.

36 Shepardson, H. C., and Shapiro, E. The Diabetes of Bearded Women (Suprarenal Tumor, Diabetes, and Hirsutism). A Clinical Correlation of the Function of the Suprarenal Cortex in Carbohydrate Metabolism, *Endocrinology* **24** 237-252 (Feb.) 1939.

37 Bartelheimer, H. Hypophysärer Diabetes, *Deutsches Arch. f. klin. Med.* **184** 185-199, 1939.

38 Lassen, H. C. A., and Hanson, L. Investigations into the Effect of the Anterior Pituitary Extract on the Carbohydrate Metabolism in Normals and in Diabetics, *Acta med. Scandinav.* 1938, supp. 89, pp. 288-299.

39 Elmer, A. W., Giedosz, B., and Scheps, M. The Anterior Pituitary and Its Diabetogenic and Pancreatotropic (Blood-Sugar Decreasing) Activity, *Acta med. Scandinav.* **93** 487-498, 1937.

40 Gessler, C. J., Halsted, J. A., and Stetson, R. P. Effect of Estrogenic Substance on Blood Sugar of Female Diabetics After Menopause, *J. Clin. Investigation* **18** 715-722 (Nov.) 1939.

Culpepper and co-workers⁴¹ have continued Hutton's observations on the treatment of diabetes mellitus by irradiation of the pituitary and the adrenal region, with inconclusive results

Johnson and associates⁴² used tremendous doses of roentgen therapy in the treatment of experimentally induced diabetes in dogs. The doses far exceeded that which it is possible to employ for human beings and had no effect on the diabetes

Bartelheimer⁴³ wrote that attempts to treat diabetes with pituitary hormone have not yet arrived at a point at which such therapy is satisfactory for clinical application. In several instances he has succeeded in decreasing the value for blood sugar and has caused a decrease in the sugar content of the urine following the administration of androgens and estrogens

Summary—We introduced this discussion with a complete summary of Russell's review. We shall close with a briefer summary of two excellent discussions by Young⁴⁴. That author discussed the evidence at hand which would suggest that the anterior lobe of the pituitary body has several separate but related effects on carbohydrate metabolism. These are (1) an anti-insulin or glycotropic effect, which diminishes sensitivity to insulin, (2) an effect (glycostatic) on the storage of glycogen, a result closely comparable to that produced by the hormones of the adrenal cortex, (3) an effect (pancreatropic) on the islands of Langerhans, causing an increase in the number and size of the cells, (4) a diabetogenic effect, the fraction producing this result being the one which can induce permanent diabetes mellitus, and (5) a ketogenic effect (Shipley and Long⁴⁵ have suggested that the ketogenic, the growth and the diabetogenic factor all may be identical)

Finally, we recommend the reading of a symposium on carbohydrate metabolism which was published in *Endocrinology*⁴⁶. This symposium

41 Culpepper, W. L., Madden, E. E., Olson, E. C., and Hutton, J. H. Treatment of Essential Hypertension and Diabetes Mellitus by Irradiation of the Pituitary and Adrenal Regions, *Endocrinology* **22** 236-242 (Feb.) 1938

42 Johnson, J. B., Selle, W. A., and Westra, J. J. Massive Roentgen Irradiation of the Hypophysis in Experimental Diabetes, *Am. J. Roentgenol.* **39** 95-102 (Jan.) 1938

43 Bartelheimer, H. Hypophysenvorderlappen und Diabetes, *Klin. Wchnschr.* **18** 647-651 (May 6) 1939

44 Young, F. G. The Relation of the Anterior Pituitary Gland to Carbohydrate Metabolism, *Brit. M. J.* **2** 393-396 (Aug. 19) 1939, The Pituitary Gland and Carbohydrate Metabolism, *Endocrinology* **26** 345-351 (Feb.) 1940

45 Shipley, R. A., and Long, C. N. H. Studies on the Ketogenic Activity of the Anterior Pituitary. I. The Relation of Ketonaemia to Ketonuria in the Rat, II. A Method for the Assay of the Ketogenic Activity, III. The Nature of the Ketogenic Principle, *Biochem. J.* **32** 2242-2256 (Dec.) 1938

46 Cori, C. F. Glycogen Breakdown and Synthesis in Animal Tissues, *Endocrinology* **26** 285-296 (Feb.) 1940

includes a discussion of the relation of all the glands of internal secretion to carbohydrate metabolism

ROLE OF THE PITUITARY BODY IN PROTEIN AND FAT METABOLISM

Studies on the relation of the anterior lobe of the pituitary body to metabolism have been extensive. The usual difficulties in interpreting these results have been encountered because of the marked variation which occurs with different species, nutritional circumstances, the time of year the study was made, the type of hormones injected and other factors. Phillips and Robb⁴⁷ have confirmed Cori's observations concerning the delayed intestinal absorption of dextrose in the hypophysectomized rat. This fact should be kept in mind in interpreting studies of metabolism which involve feeding by mouth. Mirsky⁴⁸ has reported a study of the relation of the anterior lobe of the pituitary body to protein metabolism following the administration of a crude alkaline extract. He observed a decreased rate of protein breakdown of normal dogs and an increase in the rate of protein catabolism in depancreatized dogs. The suggestion is made that the anterior lobe of the pituitary body exerts a direct effect on muscle, an effect which is in opposition to that observed in the intact animal. It is postulated that the synthesis of muscle protein consequent to the administration of extracts of the anterior lobe of the pituitary body may be dependent on the simultaneous stimulation of the pancreas. Goldzieher⁴⁹ studied the relation of the anterior lobe of the pituitary body to the specific dynamic action of protein. After the intake of a large protein meal the specific dynamic action of protein is present but is lower in hypophysectomized animals (Houssay). Goldzieher commented on the fact that in clinical examples of "hyperpituitarism" (by which term he referred to menopausal and castration states) there is evidence of a "high normal and increased dynamic action." He noted an increase in specific dynamic action in obese diabetic patients and absence of specific dynamic action in the presence of acute infections, but he found no evidence that the function of the thyroid gland has any influence on production of heat subsequent to stimulation with protein. He concluded that the thyrotropic hormone cannot be the means by which the pituitary body affects the specific dynamic action. An increase in the production of heat after the ingestion of protein occurs

47 Phillips, R. A., and Robb, P. D. Metabolism Studies in the Albino Rat Carbohydrate Studies After Hypophysectomy, *Endocrinology* **25** 187-192 (Aug.) 1939

48 Mirsky, I. A. The Influence of the Anterior Pituitary Gland on Protein Metabolism, *Endocrinology* **25** 52-56 (July) 1939

49 Goldzieher, M. A. Relation of the Anterior Lobe to the Specific Dynamic Action of Protein. A Research Nerv. & Ment. Dis., *Proc.* (1936) **17** 536-546, 1938

largely in the liver and is only indirectly influenced by a deficiency or an excess of hormone of the anterior lobe of the pituitary body

The influence of anterior pituitary extract on the proteins of the liver has been studied by Houchin⁵⁰ He found that the injection of pituitary extracts did not cause true hypertrophy of the entire liver The percentage of water did not vary significantly in the treated subjects as compared with similar percentages in untreated controls The alkali-soluble protein of the liver was decreased by a principle present in the anterior lobe of the pituitary body This decrease of the protein fraction was between 35 and 53 per cent of the normal *An increase was observed in the protein fraction containing insoluble proteins and proteins that originally were soluble in water or dilute salts, also noted was an increase in soluble nonprotein materials This hormone, Houchin stated, is entirely separate from any of the other metabolic hormones of the pituitary body, and he termed it a "protein metabolism hormone"

Schrire and Sharpey-Schafer⁵¹ found that the administration of thyrotropic extract increases the elimination of urinary creatine by stimulating the thyroid gland to increased activity The excretion of creatinine is unaffected Gonadotropic extract increases the excretion of creatinine without affecting creatine Gonadotropic substances from urine and from blood serum have no effect The factor influencing the elimination of creatinine appears to be inseparable from the pituitary gonadotropic principle Pizzolato and Beard⁵² injected various hormonal preparations into normal and into castrated rats and studied the effect of these injections on creatine-creatinine metabolism They suggested a possible synergistic action of the hormones in the body on creatin-creatinine metabolism Koven and Beard⁵³ also reported the effect of the injection of sex hormones on creatine and creatinine metabolism

Cope and his associates⁵⁴ studied the relation of the pituitary body to amylase activity In a dog with intact anterior pituitary tissue and permanent diabetes insipidus resulting from ablation of the posterior lobe of the pituitary body and stalk, there was no change in amylase activity in the blood serum Loss of the posterior lobe was therefore excluded

50 Houchin, O B The Influence of Anterior Pituitary Extracts on the Proteins of the Liver, *Endocrinology* **25** 759-767 (Nov) 1939

51 Schrire, I, and Sharpey-Schafer, E P Observations on Pituitary Control of Creatine and Creatinine Excretion, *Clin Sc* **3** 369-376 (Dec) 1938

52 Pizzolato, P, and Beard, H H Creatine-Creatinine Metabolism and the Hormones, *Endocrinology* **24** 358-363 (March) 1939

53 Koven, A L, and Beard, H H Creatine-Creatinine Metabolism and the Hormones II Progesterin and Antuitrin-T, *Endocrinology* **25** 221-226 (Aug) 1939

54 Cope, O, Kapnick, I, Lambert, A, Pratt, T D, and Verlot, M G Endocrine Function and Amylase Activity III Further Observations of Blood Serum Amylase Activity in Relation to Pituitary, Pancreas and Thyroid Function in the Dog and Rabbit, *Endocrinology* **25** 248-256 (Aug) 1939

as the source of the increase in amylase activity previously described as following total hypophysectomy. According to the observations of those investigators, injection of extract of the anterior lobe of the pituitary body into the normal dog causes a decrease in amylase activity in the blood serum. The decrease in amylase activity in acidosis following pancreatectomy in the dog and the increase to normal after the administration of insulin are confirmed. In the pancreatectomized hypophysectomized dog, amylase activity remains within normal limits. The absence of effect of insulin on amylase activity in the serum of the normal animal is not confirmed. Insulin hypoglycemia, maintained for more than six hours, results in a decrease in activity in dogs and rabbits. If hypoglycemia is maintained in the dog, the value reached in thirty-six hours is comparable to that seen in the presence of diabetic acidosis. Thyroidectomy and the administration of thyroxin produce in the dog and rabbit only a greater variation of activity of the serum amylase system. No consistent variation or tendency was encountered in their series. Removal of the pituitary body in the rabbit results in a slight decrease in serum amylase activity, in contrast to the increase encountered in the hypophysectomized dog. The significance of the difference in behavior of the serum amylase system of the dog and of the rabbit in relation to the loss of hormones of the anterior lobe of the pituitary body and adrenal cortex is discussed. It is suggested that the various hormones which influence the serum amylase system do so indirectly. The conclusion is drawn that those endocrine glands which are intimately related to carbohydrate metabolism affect the serum amylase system.

Thompson,⁵⁵ in studying the relation of the anterior lobe of the pituitary body to the metabolism of acetone bodies, found that the role of the pituitary body in carbohydrate metabolism (as related to diabetes mellitus) is not clear. He stated

I should prefer to suppose as a working hypothesis that pituitary hormone or hormones promote processes of gluconeogenesis accompanied by acetone formation either from glycerol and fatty acids of fats, respectively, or from sugar forming and acetone forming amino acids, or both, that hypophysectomy thus lessens the supply of new carbohydrate in the fasting or in the diabetic animal, and simultaneously decreases the likelihood of acetonuria, that the acetone bodies may be so produced more rapidly than they can be destroyed, whereas this will hardly be true of the sugar unless insulin is lacking, and that the pituitary either acts through the adrenal cortex or requires the presence of a cortical hormone in the circulation in order to exert its own direct control of gluconeogenesis effectively.

Shipley and Long⁴⁵ discussed the preparation of an extract which has a definite ketogenic activity. This extract did not affect the fed rat, but did affect the fasting rat. They concluded that the inhibitory action of anterior pituitary extract on the catabolism of carbohydrate and

55 Thompson, D. L. The Anterior Pituitary and the Metabolism of Acetone Bodies, *A Research Nerv & Ment Dis*, Proc (1936) **17** 257-267, 1938

protein offers satisfactory explanation for the ketosis that follows the injection Gray ⁵⁶ reviewed the results of previous workers concerning variations of ketonuria with respect to season, sex and pregnancy When the high fat diet was administered, a greater ketogenic response was found in fasting male rats than in fasting female rats, whereas the increase in liver fats was greater in female rats Evidence is presented that a large ketogenic response to administration of extract of the anterior lobe of the pituitary body is accompanied by a small increase in liver fat, and that the converse of this is also true

Campbell ⁵⁷ presented a method of assaying the potency of an extract of the anterior lobe of the pituitary body which increases the liver fat Best and Campbell ⁵⁸ described the effect of this extract on the liver fat in various animals They studied the results both of fasting alone and of the administration of extract of the anterior pituitary lobe to fasting animals, and they determined urinary ketone bodies, liver fat and body fat Fasting alone effected a pronounced increase in liver fat, there was an increase in the amount of liver fat following injection of the extract An increase in the weight of the liver of the animals receiving injection was found to be referable chiefly to the deposition of water and fat A slight increase in nonfatty solid material also occurred

Houchin and Turner ⁵⁹ studied the relation of the pituitary body to the blood lipids They used rabbits as test animals In one group they injected the extract intraperitoneally and found a gradual decline in the amount of blood lipids, the decline reached an average of about 36 per cent below the initial sample within six to eight hours and was followed by a return to approximately normal values after twenty-four hours Similar results were obtained in a group of fasting rabbits Using a pituitary extract which was rich in lactogenic hormone and in the hormone or hormones affecting carbohydrate metabolism as well as in the thyrotropic and the gonadotropic hormones, they found no influence on the lipids, nor was there any comparable effect following the injection of epinephrine, cortical extract or thyroxin Thyroxin did begin to depress the blood fats after twenty-four hours In a subsequent article, Houchin and Turner ⁶⁰ outlined the method for assaying this hormone of fat metabolism

56 Gray, C H Determination of the Ketogenic Activity of Extracts of Endocrine Organs, *Biochem J* **32** 743-755 (April) 1938

57 Campbell, J A Method of Assaying the Potency of Anterior Pituitary Extracts Which Increase Liver Fat, *Endocrinology* **23** 692-702 (Dec) 1938

58 Best, C H, and Campbell, J The Effect of Anterior Pituitary Extracts on the Liver Fat of Various Animals, *J Physiol* **92** 91-110 (Feb 16) 1938

59 Houchin, O B, and Turner, C W The Relation of the Pituitary to Blood Lipids, *Endocrinology* **24** 638-644 (May) 1939

60 Houchin, O B, and Turner, C W A Method of Assay for the Fat Metabolism Hormone of the Anterior Pituitary, *Endocrinology* **25** 216-220 (Aug) 1939

Neufeld and Collip⁶¹ reported on a fraction prepared from the anterior lobe of the pituitary body which was demonstrated to have certain physiologic properties. They stated

Results reported herein indicate that there is obtainable from pituitary tissue a fraction which is thermostable within a wide range of pH . This fraction has been demonstrated to have the following physiological properties: *a*) Production of ketonemia in both normal and adrenalectomized rats; *b*) Production of increased glycosuria and ketonuria in the Houssay dog; *c*) An antagonistic action on the hypoglycemic action of insulin, and on the hyperglycemic action of adrenalin; *d*) A glycostatic action which has been demonstrated in rats, guinea pigs and rabbits.

Later, those authors (Neufeld and Collip⁶²) discussed the effects of pituitary extract on ketonuria, fat content and fat distribution in the liver and tissues of mice.

Collip⁶³ has obtained an extract from the anterior lobe of the pituitary body which he said he considered to be the specific metabolic principle of the pituitary gland, on parenteral administration it causes an increase in the consumption of oxygen. He stated that this principle has been distinguished from most of the other well known principles, including the melanophore-expanding substance of the pars intermedia. The effect is produced almost immediately and has a relatively short duration. Rabinowitch and associates⁶⁴ discussed the influence of Collip's hormone on basal metabolism in man, following the work of O'Donovan and Collip⁶⁵. Rabinowitch and co-workers expressed the opinion that this hormone appears to be independent of thyrotropic, adrenotropic and growth hormones and that although it is obtainable from the pars intermedia and the posterior lobe of the pituitary body, it is distinguishable from the pressor and oxytocic principles. Another report of this work has been published by Billingsley, O'Donovan and Collip,⁶⁶ in which they suggested a method for assaying this principle.

61 Neufeld, A. H., and Collip, J. B. Studies of the Effects of Pituitary Extracts on Carbohydrate and Fat Metabolism, *Endocrinology* **23** 735-746 (Dec) 1938.

62 Neufeld, A. H., and Collip, J. B. The Effect of Pituitary Extracts on Ketonuria, Fat Content and Fat Distribution in the Liver and Tissues of Mice, *Endocrinology* **25** 768-774 (Nov) 1939.

63 Collip, J. B. Results of Recent Studies on the Specific Metabolic Principle of the Pituitary Gland, *Tr. A. Am. Physicians* **54** 302-303, 1939.

64 Rabinowitch, I. M., Mountford, M., O'Donovan, D. K., and Collip, J. B. Influence of a Specific Hormone of the Pituitary on the Basal Metabolism in Man, *Canad. M. A. J.* **40** 105-107 (Feb) 1939.

65 O'Donovan, D. K., and Collip, J. B. The Specific Metabolic Principle of the Pituitary, and Its Relation to the Melanophore Hormone, *Endocrinology* **23** 718-734 (Dec) 1938.

66 Billingsley, L. W., O'Donovan, D. K., and Collip, J. B. The Specific Metabolic Principle of the Pituitary, *Endocrinology* **24** 63-68 (Jan) 1939.

Summary—Evidence is reported to suggest that extracts of the anterior lobe of the pituitary body are responsible for the deposition of fat in the liver and are related to the production of ketone bodies. There is insufficient evidence which can be used as a basis for description of specific hormones for these effects. Moreover it cannot be said that there is any specific hormone responsible for protein metabolism, all that is known is that the pituitary body aids in protein synthesis. The status of a "specific metabolic hormone" is uncertain.

THYROTROPIC HORMONE

Selye⁶⁷ has reviewed the literature on the thyrotropic and the adrenotropic hormone published prior to 1938.

Uotila⁶⁸ has emphasized the role of the pituitary stalk in the regulation of the anterior lobe of the pituitary body with special reference to the thyrotropic hormone. After section of the pituitary stalk in rats, enough thyrotropic hormone is produced to keep the thyroid gland histologically normal under ordinary conditions. However, section of the stalk followed by exposure to cold prevents increased secretion of the thyrotropic hormone and hypertrophy of the thyroid gland, which normally occur in intact animals on exposure to cold. This negative effect is not the result of general pituitary insufficiency. Hence it follows that in animals exposed to prolonged cold the hypothalamus stimulates the secretion of thyrotropic hormone by impulses transmitted through the pituitary stalk. The role of the pituitary stalk in this regulation is more important than that of the cervical sympathetic nerves. After section of the pituitary stalk in rats, the testicles and seminal vesicles remain normal but the usual damaging effect of cold on spermatogenesis is abolished. Hence, the influence of temperature on the secretion of gonadotropic hormones must be, to a certain extent, under hypothalamic control. Section of the pituitary stalk does not significantly affect the growth of rats. The anterior lobe of the pituitary body appears to have a basic secretory rhythm which is independent of the pituitary stalk under ordinary conditions and which is largely under humoral influences. Nevertheless, available evidence indicates that the hypothalamus and pituitary stalk participate in the regulation of secretion by the anterior lobe of the pituitary body in specific adjustments to certain environmental situations. In the present experiments, for example, evidence was adduced to indicate the mediation of stimuli through the stalk on prolonged exposure of the animal to cold.

67 Selye, H. The Thyrotropic and Adrenotropic Hormones, *A Research Nerv & Ment Dis*, Proc (1936) **17** 239-246, 1938.

68 Uotila, U. U. On the Role of the Pituitary Stalk in the Regulation of the Anterior Pituitary, with Special Reference to the Thyrotropic Hormone, *Endocrinology* **25** 605-614 (Oct.) 1939.

Efforts have been made to assay the amount of thyrotropic hormone, and Smelser⁶⁹ has reported his method of utilizing chicks for such assay. The effect of injection of thyrotropic extract on the weight of the thyroid gland of the day old chick was studied and compared with the results of other methods of testing for this hormone. The thyroid gland of the chick is an exceedingly sensitive medium for testing for this material, reacting to one-tenth the amount required to affect the weight of the thyroid gland in the guinea pig. Weight of the thyroid gland in the chick increases with the amount of hormone injected over a wide range of doses, whereas weight of the thyroid gland in the guinea pig increases over a narrow range of doses. Response of the thyroid gland of the chick is consistent, significant values being obtainable with small groups. Administration of the total dose of thyrotropic extract in multiple injections greatly increases the response. Crude nonpituitary extracts and urine and blood serums do not affect weight of the thyroid gland in chicks. Weight of the thyroid gland of normal guinea pigs is exceedingly variable, even when considered in terms of body weight, thus requiring that animals used for assay be within a narrow weight range. Histologic response is elicited by amounts of extract too small to produce hypertrophy and is, therefore, the more sensitive test, although not so adaptable to quantitative assay. If it is desired to demonstrate small amounts of thyrotropic principle, both histologic structure and weight of the thyroid gland should be taken as criteria of an effect. A statistical treatment of data obtained at assay is advocated. Bergman and Turner⁷⁰ have compared methods of assay of thyroid glands in the guinea pig and in the chick and have found the male chick unit of thyrotropic hormone to be about a fourth the amount of the guinea pig unit. On an equal bodily basis the male chick is only slightly more sensitive than the guinea pig. In a related paper, Turner and Cupps⁷¹ reported the use of the chick assay method to determine the amount of thyrotropic hormone in the pituitary body of the albino rat during growth, pregnancy and lactation. The concentration of the thyrotropic factor in the pituitary body of both sexes increased during the period of rapid growth. However, the pituitary bodies of the female rats contained only about 50 per cent as much hormone as those of the male rats during this period. In a comparison of all weight groups, it was

69 Smelser, G. K. Chick Thyroid Responses as a Basis for Thyrotropic Hormone Assay, *Endocrinology* **23** 429-438 (Oct.) 1938

70 Bergman, A. J., and Turner, C. W. A Comparison of the Guinea Pig and Chick Thyroid in the Assay of the Thyrotropic Hormone, *Endocrinology* **24** 656-664 (May) 1939

71 Turner, C. W., and Cupps, P. T. The Thyrotropic Hormone in the Pituitary of the Albino Rat During Growth, Pregnancy and Lactation, *Endocrinology* **24** 650-655 (May) 1939

observed that the pituitary body of the female rat contained 62 per cent as much as the pituitary body of the male rat per gram of fresh tissue. In the estrous female rat the concentration of the hormone was low and continued so during the first half of pregnancy. There was evidence of a definite increase in the concentration of the hormone during the latter part of pregnancy and of an additional 40 per cent increase during lactation.

Jones ⁷² has studied the amount of thyrotropic hormone excreted in the urine by patients suffering from different conditions, he assayed the hormone by the chick assay method. Urine obtained from 2 patients who had myxedema, 1 who had postoperative hypothyroidism and 2 who had acromegaly was tested for thyrotropic activity, 1 specimen of urine (from a patient who had myxedema) gave results suggesting possible thyrotropic activity. Serums from 9 schizophrenic patients did not show any antithyrotropic activity when injected into chicks in association with known amounts of the thyrotropic substance.

Hundhausen ⁷³ studied the effect of decreased intake of food on the thyroid gland and on the thyrotropic hormone of the anterior lobe of the pituitary body, and concluded that the changes which result (arrest of the activity of the thyroid gland and a decrease in the thyrotropic hormone of the pituitary body) are related to deficiency of vitamin B₁ rather than to limitation of intake of food, for rats maintained on a qualitatively adequate diet of half the usual amount do not exhibit these changes.

Canzanelli and Rapport ⁷⁴ studied the effect of thyrotropic hormone alone and with other substances on the consumption of oxygen by the thyroid gland and the liver in vitro. They concluded that the action of the thyrotropic hormone on metabolism, through the thyroid gland, is not exerted by virtue of a specific effect on thyroxin, thyroglobulin or diiodotyrosine. Thyrotropic hormone plus thyroid tissue after being incubated for four hours with guinea pig liver depressed the consumption of oxygen by the liver, as did thyroid tissue alone.

Merten and Hinsberg ⁷⁵ studied the effect of ultrafiltrable and thyrotropic extracts of the anterior lobe of the pituitary body on carbohydrate

⁷² Jones, M. S. A Study of Thyrotropic Hormone in Clinical States, *Endocrinology* **24** 665-671 (May) 1939.

⁷³ Hundhausen, G. Ueber den Einfluss verminderter Nahrungszufuhr auf Schilddrüse und thyreotropes Hormon des Hypophysenvorderlappens, *Arch. f. exper. Path. u. Pharmacol.* **192** 634-638, 1939.

⁷⁴ Canzanelli, A., and Rapport, D. The Effect of Thyrotropic Hormone, Alone and with Other Substances, on the In Vitro O₂ Consumption of Thyroid and Liver, *Endocrinology* **22** 73-79 (Jan.) 1938.

⁷⁵ Merten, R., and Hinsberg, K. Hypophysenvorderlappen und Kohlehydratstoffwechsel, Ueber die verschiedenartige Beeinflussung des Kohlehydratstoffwechsel durch Ultrafiltrate und Thyreotropwirksame Hypophysenvorderlappenextrakte, *Klin. Wchnschr.* **18** 901-905 (June 30) 1939.

metabolism They found that the thyrotropic hormone is sensitive to heat and that it is not ultrafiltrable through filters impermeable to albumin The hormone of the carbohydrate metabolism is ultrafiltrable and relatively thermostable Ultrafiltrates of previously potent thyrotropic extract show no effect on the thyroid gland in guinea pigs

Clinical Aspects—Thompson and associates⁷⁶ reported the production of hyperthyroidism in man by the subcutaneous injection of an extract of the anterior lobe of the pituitary body They were able to increase the metabolic rate from 20 to 30 per cent above normal and to produce all the symptoms of hyperthyroidism, including an increase in the size of the thyroid gland When this extract was injected into patients suffering from exophthalmic goiter, there was an increase in both the signs and the symptoms of this disease The effect was only temporary, and with continued treatment the basal metabolic rate decreased, sometimes to less than the original figure No response occurred in patients suffering from total myxedema There was an increase in the basal metabolic rate in patients who had moderate hypothyroidism (but with functioning thyroid tissue) This is further evidence of the fact that the thyrotropic hormone is dependent on a functioning thyroid gland for its activity These observations were also made by Sharpey-Schafer and Schrire⁷⁷

Harrison⁷⁸ used thyrotropic hormone for 5 patients and studied its effect on blood cholesterol The value for cholesterol was reduced in 2 patients who had low basal metabolic rates without myxedema, in 1 who had questionable myxedema and in 1 who had true myxedema It did not cause any reduction in the value for blood cholesterol in another patient with true myxedema

Emerson and Cutting⁷⁹ have attempted to assay the amount of thyrotropic hormone contained in the urine Urinary thyrotropic activity could not be demonstrated in normal human beings or in normal animals, and could be demonstrated only rarely in human beings with hyperthyroidism Transient urinary thyrotropic activity regularly followed thyroidectomy in animals and man, but could be demonstrated

76 Thompson, W O, Thompson, P K, Taylor, S G, III, and Dickie, L F N The Production of Hyperthyroidism in Man with Pituitary Extracts, *Tr A Am Physicians* **53** 243-244, 1938, Influence of Pituitary in Thyroid Disease, *West J Surg* **47** 4-9 (Jan) 1939

77 Sharpey-Schafer, E P, and Schrire, I The Effect of Pituitary Thyrotropic Extract on Subjects with Low Basal Metabolic Rates, *Quart J Med* **8** 195-208 (July) 1939

78 Harrison, K S Clinical Application of Thyreotropic Hormone, *M J Australia* **1** 681-686 (May 6) 1939

79 Emerson, K, Jr, and Cutting, W C Urinary Thyrotropic Hormone, *Endocrinology* **23** 439-445 (Oct) 1938

only rarely in the presence of spontaneous hypothyroidism. In a subsequent paper Cutting, Robson and Emerson⁸⁰ reported refractoriness arising from administration of pituitary thyrotropic extracts and stated that they had much less evidence of refractoriness arising from the flavianate method of preparation from fresh pituitary bodies.

Grumbrecht and Loeser⁸¹ injected thyrotropic hormone into pregnant guinea pigs and thereby caused fetal deaths.

Murphy and associates⁸² reported hypertrophy of the heart and kidneys following the injection of thyrotropic hormone. This action was enhanced by "dye-blocking" the reticuloendothelial tissues previous to and during the period of injection.

Zeus⁸³ found definite evidence of cardiac dilatation, hypertrophy and degeneration of the heart in animals which had received similar injection (but without attention to the reticuloendothelial system).

Summary—The thyrotropic hormone is one of the best established of all the pituitary hormones. The changes which occur in the thyroid gland following hypophysectomy are definite, as are those which can be produced by the experimental injection of an extract containing the hormone. There is ample clinical evidence to suggest the action of the pituitary body on the thyroid gland, as is often seen in the hyperthyroidism of acromegaly. The time may come when the thyrotropic hormone will be of clinical importance, the time is not yet.

ROLE OF THE ANTERIOR LOBE OF THE PITUITARY BODY WITH RESPECT TO THE MAMMARY GLAND

Riddle and Bates⁸⁴ commented on Kuizrock's report concerning the use of the lactogenic hormone in the treatment of women whose lactation was subnormal. They considered the term "lactogenic hormone" to be incorrect, since (1) lactogenic activity is only one of the physiologic properties of the hormone, (2) it depresses the activity of the gonads by blocking the release of gonadotropic pituitary hormone, (3) it causes splanchnomegaly in some animals, (4) it has some effect on growth and probably has an action on functioning adrenal cortex, (5) it has

80 Cutting, W. C., Robson, G. B., and Emerson, K., Jr. Refractoriness from Pituitary Thyrotropic Extracts, *Endocrinology* **24** 739-740 (May) 1939.

81 Grumbrecht, P., and Loeser, A. Fruchtlos durch thyreotropes Hormon der Hypophyse, *Klin. Wchnschr.* **17** 233-235 (Feb. 12) 1938.

82 Murphy, R., Lowther, S. W., and Pagniello, L. Organ Hypertrophy Following Injections of Thyrotropic Hormone, *Am. J. Physiol.* **124** 110-113 (Oct.) 1938.

83 Zeus, L. Ueber tierversperimentelle Herzbeeinflussung durch Verabfolgung von thyreotropem Hormon, *Arch. f. Kreislaufforsch.* **4** 49-68 (Feb.) 1939.

84 Riddle, O., and Bates, R. W. Prolactin, A Research Nerv. & Ment. Dis., *Proc.* **17** 287-297, 1938.

calorigenic action even in thyroidectomized animals, and (6) it probably shares in the diabetogenic response. Present extracts of this hormone are not free of intermediate hormones of the posterior lobe of the pituitary body, gonadotropic and thyrotropic hormones.

Folley⁸⁵ suggested that the term "prolactin" be reserved for the factor of the anterior lobe of the pituitary body that stimulates growth of the crop gland. He also wrote that the factor has not necessarily been shown to exert true lactogenic activity in mammals, and he pointed out that the circumstance that an extract of the pituitary body causes a few drops of fluid having the superficial appearance of milk to appear in rabbits or rats is not satisfactory evidence that the extract is truly lactogenic. He recalled previous work which indicates that the ability to stimulate lactation in cows is closely correlated with the glycotropic activities of the preparation rather than with the crop-stimulating activity. Folley and Young⁸⁶ studied the effect of anterior pituitary extract on established lactation in cows. They concluded that there is no evidence that a single lactation hormone is secreted by the anterior lobe of the pituitary body and suggested that the term be omitted from the literature. Folley⁸⁷ has likewise studied interactions of estrogen and prolactin with special reference to the effect of estrogen on the glandular response of the crop of the pigeon. He discussed the ability of estrogen to inhibit the crop-stimulating potency of this pituitary principle. Folley⁸⁸ has also reported a study of sex differences in the response of the crop glands of pigeons to prolactin and has obtained the most marked response in pigeons in which the gonads were undeveloped.

Li and his associates⁸⁹ presented evidence to indicate that primary amino groups are essential to the specific activity of the lactogenic hormone.

85 Folley, S. J. The Role of the Anterior Pituitary in Lactation. A Review of Recent Work, *Lancet* **2** 389-390 (Aug. 13) 1938.

86 Folley, S. J., and Young, F. G. Effect of Anterior Pituitary Extract on Established Lactation in Cow, *Proc. Roy. Soc., London, s. B* **126** 45-76 (Sept. 23) 1938, Effect of Continued Treatment with Anterior Pituitary Extracts on Milk Volume and Milk-Fat Production in Lactating Cow, *Biochem. J.* **33** 192-197 (Feb.) 1939.

87 Folley, S. J. Interactions of Estrone and Prolactin with Special Reference to the Effect of Estrone on the Pigeon Crop-Gland Response, *Endocrinology* **24** 814-822 (June) 1939.

88 Folley, S. J. Sex Difference in Response of the Pigeon Crop-Gland to Prolactin, *Nature, London* **144** 834 (Nov. 11) 1939.

89 Li, C. H., Lyons, W. R., Simpson, M. E., and Evans, H. M. Essentiality of Primary Amino Groups for Specific Activity of the Lactogenic Hormone, *Science* **90** 376-377 (Oct. 20) 1939.

Turner and co-workers⁹⁰ have postulated evidence for the presence in the pituitary body of a mammary gland-stimulating factor not associated with the lactogenic hormone. This has been termed the "mammo-genic hormone." They presented physiologic and chemical observations indicating the separate identity of this hormone and outlined a method for its assay.

Wiegand⁹¹ and Ehrhardt and Voller⁹² have reported observations on the influence of ovarian function on the lactogenic hormone. Reece and Mixner⁹³ studied the effect of testosterone on the pituitary body and the mammary glands. They reported that daily injections of testosterone in sexually mature spayed rats augmented the lactogenic content of the pituitary body by 40 per cent. These injections caused no change in the weight of pituitary bodies. They induced extensive development of the alveolar system of the mammary gland and initiated secretory activity. The authors concluded that the effect of testosterone is to stimulate the pituitary body to secrete and discharge the lactogenic hormone.

Lacassagne and Chamorro⁹⁴ subjected hypophysectomized male mice to weekly injections of crystallized estrogen. None showed any development of the mammary glands. Others received weekly injections of estradiol benzoate, starting a few days after birth of the animals. Two or three months later the breasts of these animals showed marked cystic hyperplasia. Hypophysectomy performed at this time produced rapid regression of breasts, which atrophied in a few weeks. Hypophysectomy performed on animals suffering from carcinoma of the breast produced temporary retardation in the growth of the tumor.

90 Gomez, E. T., and Turner, C. W. Further Evidence for a Mammogenic Hormone in the Anterior Pituitary, *Proc Soc Exper Biol & Med* **37** 607-609 (Jan) 1938. Lewis, A. A., and Turner, C. W. Chemical Concentration of Mammogen from Prehypophyseal Tissue, *ibid* **39** 435-436 (Dec) 1938. Bergman, A. J., Turner, C. W., and Cupps, P. T. Are the Lactogenic and Carbohydrate Metabolism Hormones Identical? *Endocrinology* **23** 228-232 (Aug) 1938. Lewis, A. A., Turner, C. W., Gomez, E. T., and Carroll, W. T. The Biological Assay of the Mammogenic Duct Growth Factor of the Anterior Pituitary, *ibid* **24** 157-164 (Feb) 1939.

91 Wiegand, M. Ueber den Einfluss der Ovarialfunktion auf die laktogene Wirkung der Hypophyse, *Arch f Gynak* **165** 149-154, 1937.

92 Ehrhardt, K., and Voller, H. F. Untersuchungen uber das Laktations-hormon des Hypophysenvorderlappens, *Endocrinologie* **22** 19-24 (July) 1939.

93 Reece, R. P., and Mixner, J. P. Effect of Testosterone on Pituitary and Mammary Gland, *Proc Soc Exper Biol & Med* **40** 66-67 (Jan) 1939.

94 Lacassagne, A., and Chamorro, A. Consequences de l'hypophysectomie chez des souris sujettes au carcinome mammaire traitees par hormone oestrogene. *Compt rend Soc de biol* **131** 1077-1078, 1939.

Clinical Aspects—Ross⁹⁵ reported on the use of prolactin for lactating mothers when the secretion of breast milk on the fifth and the sixth postpartum day was less than 400 cc. He reported definite improvement in the condition of the patients as arising from the use of this hormone. Somewhat similar reports have been published by Stewart and Pratt⁹⁶ and by Kenny and associates⁹⁷.

Weiner⁹⁸ reviewed the clinical use of this hormone and reported the appearance of definite local reaction to the injection. He concluded that at present preparations of prolactin for clinical use are not sufficiently pure to warrant their use for human beings.

Beilly and Solomon⁹⁹ studied 108 cases in which they sought to inhibit lactation by means of administration of testosterone. Complete inhibition occurred in 58 per cent of the cases and incomplete inhibition in 40 per cent of the cases. Failure occurred in 2 per cent. Stephens¹⁰⁰ suppressed lactation in a female acromegalic patient by the administration of an estrogenic substance.

Summary—The effects of extracts of the anterior lobe of the pituitary body on the mammary gland need critical consideration. The role of psychic influences on the secretion of breast milk, the presence of nutritional deficiencies and perhaps other factors must be evaluated before it can be assumed that preparations of the anterior lobe exert true lactogenic action. There are as yet no preparations of the anterior lobe of the pituitary body with proved lactogenic action suitable for routine use for the human being.

EFFECT OF THE ANTERIOR LOBE OF THE PITUITARY BODY ON GROWTH PHENOMENA

There continues to be discussion regarding the actuality of a single growth hormone. Evans and his group¹⁰¹ have submitted additional

95 Ross, J. R. Prolactin. Its Effect on the Secretion of Woman's Milk, *Endocrinology* **22** 429-434 (April) 1938.

96 Stewart, H. L., Jr., and Pratt, J. P. Effect of Prolactin on Mammary Gland Secretion, *Endocrinology* **25** 347-353 (Sept.) 1939.

97 Kenny, M., King, E., Evers, N., and Hurran, W. J. Effect of Prolactin on Lactation in Nursing Women, with Notes on Preparation of Prolactin, *Lancet* **2** 828-831 (Oct. 14) 1939.

98 Werner, A. A. Lactogenic Hormone. Severe Reactions from Its Use, *Endocrinology* **24** 119-121 (Jan.) 1939.

99 Beilly, J. S., and Solomon, S. The Inhibition of Lactation Post-Partum with Testosterone Propionate, *Endocrinology* **26** 236-240 (Feb.) 1940.

100 Stephens, D. J. Suppression of Lactation in Acromegaly During Estrogenic Therapy, *Endocrinology* **25** 638-641 (Oct.) 1939.

101 Evans, H. M., Uyei, N., Bartz, Q. R., and Simpson, M. E. The Purification of the Anterior Pituitary Growth Hormone by Fractionation with Ammonium Sulfate, *Endocrinology* **22** 483-492 (April) 1938. Meamber, D. L.,

evidence to support their contention that the growth hormone is a specific hormone, and have reported that they have prepared a hormone free from lactogenic and thyrotropic effect. They have been able to promote growth in excess of the normal by injecting extract of the anterior lobe of the pituitary body in thyroidectomized animals, but the effect on growth is much greater when the thyroid gland is present. Thyroxin, of course, promotes the growth of thyroidectomized animals, but it does not have this effect when it is administered to thyroidectomized and hypophysectomized animals. Characteristic ovarian changes are found in animals which have been deprived of the thyroid glands for long periods, and these changes can be relieved by the administration of thyroxin but not by the injection of pituitary hormones. Salmon¹⁰² implanted pituitary bodies in newborn thyroidectomized and parathyroidectomized rats after weaning time and failed to observe any response in growth in those animals in which thyroidectomy had been completed. The only observed response in growth occurred in those animals in which remnants of thyroid tissue were demonstrable.

Chou and associates¹⁰³ reported observations on the quantitative assay of the growth-promoting extract of the hypophysis. They noted a marked difference in response among the various sex and age groups. In percentile increase in weight, the sensitivity of the hypophysectomized rat is probably more than twice that of the normal adult female rat. Likewise, variation in size of the dose produces a clearer difference in response in the hypophysectomized rat. In the normal animal, unlike the effect in the hypophysectomized rat, a variation in dose of 100 per cent often fails to produce a convincing difference in response. The normal female rat is more sensitive than the normal male rat. In the series reported on by those authors, the response both of normal and of hypophysectomized rats after a rest period of two to six weeks was less if the extract had been given previously.

Lee¹⁰⁴ has studied the relation of the anterior lobe of the pituitary body to protein metabolism. He pointed out that the most characteristic

Fraenkel-Conrat, H. L., Simpson, M. E., and Evans, H. M. The Preparation of Pituitary Growth Hormone Free from Lactogenic and Thyrotropic Hormones, *Science* **90** 19-20 (July 7) 1939. Evans, H. M., Simpson, M. E. and Pencharz, R. I. Relation Between the Growth Promoting Effects of the Pituitary and the Thyroid Hormone, *Endocrinology* **25** 175-182 (Aug.) 1939.

102 Salmon, T. N. The Effect on the Growth Rate of Thyro-Parathyroidectomy in Newborn Rats and of the Subsequent Administration of Thyroid, Parathyroid and Anterior Hypophysis, *Endocrinology* **23** 446-457 (Oct.) 1938.

103 Chou, C., Chang, C., Chen, G., and Van Dyke, H. B. Observations on the Quantitative Assay of Growth-Promoting Extract of the Hypophysis, *Endocrinology* **22** 322-334 (March) 1938.

104 Lee, M. O. Relation of the Anterior Pituitary Growth Hormone to Protein Metabolism, *A Research Nerv. & Ment. Dis., Proc.* (1936) **17** 193-221, 1938.

metabolic factor of growth in young animals is the active manufacture and deposition of body protein. There are a strongly positive nitrogen balance and a retention of water and minerals. This deposit and the growth process itself are similar, and both depend on the anabolic phases of amino acid metabolism. Lee said that "the growth hormone acts to create a plethora of protein deposition which allows a genetically limited process of conversion into permanent body structures to continue at its maximal youthful rate beyond the age at which it normally subsides, and causes a return toward that rate when such treatment is begun after chemical maturity has been reached." He also commented on the fact that in the fresh pituitary lobes of calves, steers and bees, concentration of the growth hormone shows no appreciable difference, therefore he concluded that the amount of hormone needed is as great in adult animals as in young animals.

Clinical Aspects—References to the treatment of pituitary dwarfism continue to appear.¹⁰⁵ The literature contains no report of any case of pituitary dwarfism in which the patient has achieved normal height by means of a pituitary hormone. Werner and associates¹⁰⁶ studied the treatment with growth hormones of children suffering from mongolism and found no evidence that injections of these factors caused any change in the patient's growth. Nothing new or important has been published concerning the diagnosis or treatment of acromegaly.

Summary—There is no unquestioned evidence in support of the view that the pituitary body elaborates a pure growth hormone. Recognition of the fact that many glands (thyroid, gonads, pineal body and others) produce hormones which are concerned with the phenomenon of growth should not be neglected. Disturbances of growth are a part of the clinical syndrome produced by the hyperfunction or hypofunction of many glandular elements. Finally, the unsatisfactory results which have followed the clinical use of "growth hormone" should be considered

105 Taylor, N. M. Pituitary Dwarfism. Treatment with Growth Hormone, *Endocrinology* **22** 707-715 (June) 1938. Buchanan, J. A., and Ballweg, H. A. A Case of Pituitary Dwarfism Treated with Antuitrin-G, *ibid* **24** 565-571 (April) 1939. Lawrence, C. H., and Harrison, A. Pituitary Dwarfism. Case Report Illustrating Response to Treatment, *ibid* **23** 360-363 (Sept.) 1938. Beck, H. G., and Suter, G. M. Pituitary Dwarfism with Diabetes Mellitus, *ibid* **22** 115-119 (Jan.) 1938.

106 Werner, A. A., Lewald, J., Johns, G. A., and Kelling, D. Growth in Children with Mongolism. A Four-Year Study of Eight Patients, *Am. J. Dis. Child* **57** 554-563 (March) 1939.

EFFECTS OF THE ANTERIOR LOBE OF THE PITUITARY BODY
ON THE ADRENAL GLANDS

Reese and associates¹⁰⁷ studied the histologic changes occurring in the anterior lobe of the pituitary body in the male rat following bilateral adrenalectomy. They found changes in all the cell types. The presence of a significant number of hyperactive basophilic cells suggested that an attempt is being made to compensate for the degenerative changes seen in other basophilic cells.

Swingle and fellow workers¹⁰⁸ injected extract of the anterior lobe of the pituitary body into adrenalectomized cats and increased the survival time, but this extract did not entirely substitute for the adrenal cortical hormone. The hormone of the corpus luteum ameliorates the symptoms of adrenal insufficiency in the dog, the ferret and the cat. Close similarity between progesterone and corticosterone probably explains the improvement which occurs in these animals in the presence of pseudopregnancy. Apparently the organism lacking adrenal tissue has the ability to convert progesterone into corticosterone. Swingle and associates concluded that it did not seem unreasonable to assume that the testes of cats contain progesterone and that the injection of extract of the anterior lobe of the pituitary body stimulates the gonad to produce excessive amounts, which in time are converted into corticosterone or related substances having activities similar to those of the cortical hormone. This opinion is supported by their observation that when extract of the anterior lobe of the pituitary body is injected into the normal cat, the health and survival time are much better than for similarly treated castrated cats. The fact that castrated cats react at all to injections of the extract of the anterior lobe of the pituitary body raises the question as to whether tissues other than gonads can form progesterone or related substances.

MacKay and Wick¹⁰⁹ studied the influence of adrenalectomy on the blood and urinary ketones during fasting and after administration of the extract of the anterior lobe of the pituitary body. They reported that adrenalectomy has little effect on the ketogenic activity of anterior pituitary extract.

107 Reese, J. D., Koneff, A. A., and Akimoto, M. B. Anterior Pituitary Changes Following Adrenalectomy in the Rat, *Anat. Rec.* **75** 373-403 (Nov. 25) 1939.

108 Swingle, W. W., Parkins, W. M., Taylor, A. R., Hays, W. H., and Morrell, J. A. Effect of Extract of Anterior Pituitary upon the Life-Span of Castrate-Adrenalectomized Cats, *Proc. Soc. Exper. Biol. & Med.* **38** 876-879 (June) 1938.

109 MacKay, E. M., and Wick, A. N. Influence of Adrenalectomy on the Blood and Urine Ketones During Fasting and Anterior Pituitary Extract Administration, *Am. J. Physiol.* **126** 753-757 (July) 1939.

Miller and Riddle ¹¹⁰ studied the effect of several pituitary hormones on adrenal cortical function. They said that the ability of pituitary extracts to stimulate cortical tissue is independent of their lactogenic, follicle-stimulating and thyrotropic potency. Androgen stimulated both the cortical and the medullary tissues in normal and in hypophysectomized pigeons. Estrogen stimulated the cortical tissue at least in the intact birds. Administration of thyroxin plus vitamin supplements elicited evidence of the ability of these substances to stimulate cortical tissues in hypophysectomized pigeons. Rosen and Marine ¹¹¹ found the presence of the thyroid gland essential to the action of anterior pituitary extracts on the adrenal glands.

Ingle ¹¹² studied the effect of administration of large amounts of extract of adrenal cortex on the adrenal cortices of normal and of hypophysectomized rats. He observed no apparent effect of the extract on the adrenal cortex and suggested support for the hypothesis that atrophy of the adrenal cortex may be referable to restriction of the output of the adrenotropic principle.

Martin and associates ¹¹³ recorded the excretion of an antidiuretic substance in the urine of adrenalectomized cats, a substance which is not present when adrenal cortical extract is administered. Sievert ¹¹⁴ described a substance obtained from the urine of 26 of 30 patients suffering from hypertension which when injected into mice was found to have an effect on the adrenal glands.

Rogoff and associates ¹¹⁵ presented additional evidence that the rate of secretion of epinephrine in the adrenal gland is not significantly altered by hypophysectomy.

110 Miller, R. A., and Riddle, O. Stimulation of Adrenal Cortex of Pigeons by Anterior Pituitary Hormones and by Their Secondary Products, *Proc Soc Exper Biol & Med* **41** 518-522 (June) 1939.

111 Rosen, S. H., and Marine, D. Inhibiting Effect of Thyroidectomy on Adrenal Cortex Hypertrophy Following Injections of Anterior Pituitary Extract, *Proc Soc Exper Biol & Med* **41** 647-650 (June) 1939.

112 Ingle, D. J. Effects of Administering Large Amounts of Cortin on Adrenal Cortices of Normal and Hypophysectomized Rats, *Am J Physiol* **124** 369-371 (Nov) 1938.

113 Martin, S. J., Herrlich, H. C., and Fazekas, J. F. Relation Between Electrolyte Imbalance and Excretion of Antidiuretic Substance in Adrenalectomized Cats, *Am J Physiol* **127** 51-57 (Aug) 1939.

114 Sievert, C. Ueber den Reizstoff der genuine Hypertension. III. Die Technik der Darstellung des blutdrucksteigernden Stoffes, seine physikalisch-chemischen Eigenschaften sowie der Nachweis der kortikotropen Substanz, *Ztschr f klin Med* **133** 261-276, 1938.

115 Rogoff, J. M., Nixon, E. N., Stewart, G. N., and Marcus, E. Epinephrine Secretion in Hypophysectomized Dogs, *Proc Soc Exper Biol & Med* **37** 715-717 (Jan) 1938.

Summary—There is a definite relation between the anterior lobe of the pituitary body and the adrenal cortex. Many of the functions of these two glands are rather similar. There is no pituitary "cortico-tropic hormone" which is suitable for human use.

GONADOTROPIC SUBSTANCES

Weil and Zondek¹¹⁶ have studied the histologic aspects of the pituitary bodies of white rats into which estrogen has been injected. They injected large amounts of estrogen into these animals and found that marked enlargement of the anterior lobe of the pituitary body resulted, the enlargement varied directly according to the dose. All three types of pituitary cells became swollen, their Golgi apparatus was markedly dilated and most of the eosinophilic cells degenerated. This effect also varied directly with the dose. The pars intermedia and pars nervosa were not directly affected, but were compressed when the anterior lobe of the pituitary body was markedly enlarged. In advanced conditions, the pars nervosa exhibited a loss of cells and an increase in the glial fibers. Phelps, Ellison and Burch¹¹⁷ studied the survival, structure and function of pituitary grafts in untreated rats and in rats into which estrogen had been injected. Results of the experiment, they said,

indicate that some, if not all, of the effects of estrogen upon the structure of the anterior lobe can be produced in the absence of the nervous connections of the pituitary. They indicate further that the anterior lobe is capable of regenerating after having undergone partial degeneration. The observations on the effect of estrogen on the survival and regeneration of the grafts afford conclusive evidence that this hormone stimulates the pituitary.

Wolfe and Wright¹¹⁸ studied the histologic effects induced in the anterior lobe of the pituitary body of the rat by the prolonged injection of estrogen, with particular reference to the production of pituitary adenomas. They studied the pituitary bodies of 37 rats which had received injections of estrogen for periods of from thirty to four hundred and twenty-five days. They found that in the rats treated for the shorter periods such injections induced marked but uniform hypertrophy of the

116 Weil, A., and Zondek, B. The Histopathology of the Pituitary of the White Rat Injected with Follicular Hormone, *Endocrinology* **25** 114-122 (July) 1939

117 Phelps, D., Ellison, E. T., and Burch, J. C. Survival, Structure and Function of Pituitary Grafts in Untreated Rats and in Rats Injected with Estrogen, *Endocrinology* **25** 227-235 (Aug.) 1939

118 Wolfe, J. M., and Wright, A. W. Histologic Effects Induced in the Anterior Pituitary of the Rat by Prolonged Injection of Estrin, with Particular Reference to the Production of Pituitary Adenomata. *Endocrinology* **23** 200-210 (Aug.) 1938

pituitary body but that in rats receiving injections for a long time adenoma was induced. The initial reaction was generalized. The chromophilic cells were markedly degenerated and reduced in number, whereas chromophobes were decidedly increased in size and number. Three types of adenoma were described. These included (1) pituitary adenomas, associated with profound vascular changes, (2) small nodular foci of cells presenting structural characteristics different from the cells of the surrounding extra-adenomatous tissue, and (3) diffuse adenomatous hyperplasia of the entire pituitary body. A vascular condition of the cells of the anterior lobe, considered to be degenerative, was described. Mitotic figures were generally more abundant in rats treated for shorter periods.

Ehrhardt and Funke¹¹⁹ observed the action of the hormone of the corpus luteum on the anterior lobe of the pituitary body.

Collip, Selye and Williamson¹²⁰ found ovarian atrophy and signet ring cells in the hypophysis following the chronic injection of extract of the anterior lobe of the pituitary body.

Wolfe and Hamilton¹²¹ studied the effect of testosterone propionate on the structure of the anterior lobe of the pituitary body of the female rat, with particular reference to the effects of prolonged administration on the numbers of cells. They found marked changes in the eosinophilic and basophilic cells.

Zondek¹²² reported the development of enormous pituitary tumors following chronic injection of estrogenic substances into rats. The duration of treatment seemed far more influential on the development of the tumors than the amount of estrogen injected. The enlarged pituitary bodies and the tumors contained the same amount of gonadotropic hormone as did the normal pituitary bodies of control animals.

Friedgood and Dawson¹²³ reported on cytologic evidence of gonadotropic activity of the anterior lobe of the hypophysis in the rabbit. They

119 Ehrhardt, K., and Funke, R. Untersuchungen über die Rückwirkung des Corpus luteum-Hormons auf den Hypophysenvorderlappen, *Klin Wchnschr* **17** 1588-1589 (Nov 5) 1938.

120 Collip, J. B., Selye, H., and Williamson, J. E. Changes in the Hypophysis and the Ovaries of Rats Chronically Treated with an Anterior Pituitary Extract, *Endocrinology* **23** 279-284 (Sept) 1938.

121 Wolfe, J. M., and Hamilton, J. B. Action of Testosterone Propionate on the Structure of the Anterior Pituitary of the Female Rat with Particular Reference to the Effects of Prolonged Administration on the Levels of Cells, *Endocrinology* **25** 572-583 (Oct) 1939.

122 Zondek, B. Hypophyseal Tumors Induced by Estrogenic Hormone, *Am J Cancer* **33** 555-559 (Aug) 1938.

123 Friedgood, H. B., and Dawson, A. B. Cytologic Evidence of the Gonadotropic Activity of the Rabbit's Anterior Hypophysis. *Endocrinology* **22** 674-686 (June) 1938.

said that they found isolated small carmine-staining cells which occur in the anterior lobe of the pituitary body of castrated and immature rabbits. The number of these cells appears to be increased in animals approaching sexual maturity and may occasionally be fairly prominent in the pituitary body of the estrous rabbit. They dominate the cytologic appearance of the gland only after mating, during which period they become markedly enlarged and increased in number. The precise relation of this cell to the pituitary hormones which are known to be secreted is as yet not clear. Many difficulties remain, they exist because of the discrepancies in various species of animals, the various ages of animals studied and similar considerations.

Diaz and associates¹²⁴ studied the effect of various gonadotropic substances on the ovaries, pituitary body and adrenal glands of animals receiving long term injections of estrogen. Injections of estrogen produced a decrease in ovarian size, with general regression of the germinal and interstitial elements. Ovaries became atrophic but responded normally to injected gonadotropic substance. After long term injections of estrogen there was marked pituitary hypertrophy with no change in the adrenal glands. Therefore, the investigators said, they felt that estrogen acts directly on the pituitary body. The ovary is not fundamentally damaged, but becomes atrophic because of inadequate stimulation.

Lauson, Golden and Elmer Sevringhaus¹²⁵ studied the gonadotropic content of the hypophysis throughout the life cycle of normal female rats. They used the pituitary bodies from 248 donors varying in age from 14 days to 2½ years. The gonadotropic content was assayed by the uterine method on 22 day old immature rats. They found that pituitary potency rises to a peak at the age of 21 days and decreases gradually until the onset of puberty, at which stage there is a rapid decrease in potency to about half the prepuberal degree of potency. Throughout adult sex life, the content of the pituitary body in the preestrous stage remains constantly at the low prepuberal level despite continued increase in the size of the pituitary body itself. This is interpreted to mean that the pituitary body in the mature animal stores little of its gonadotropic complex, but rather releases it as rapidly as it is formed. Limited study of aged animals indicates that pituitary potency markedly increases as the ovaries fail. The assumed parallel between the natural and the artificial climacteric seems reasonably established.

124 Diaz, J. T., Phelps, D., Ellison, E. T., and Burch, J. C. The Effects of Various Gonadotropic Substances upon the Ovaries, Pituitaries and Adrenals of Animals Receiving Long-Term Injections of Estrin, *Am J Physiol* **121** 794-799 (March) 1938.

125 Lauson, H. D., Golden, J. B. and Sevringhaus, E. L. The Gonadotropic Content of the Hypophysis Throughout the Life Cycle of the Normal Female Rat, *Am J Physiol* **125** 396-404 (Feb.) 1939.

Makepeace¹²⁶ studied the effect of progestin on the anterior lobe of the pituitary body. He observed the changes which progestin produced in the endometrium from the proliferative to the progestational stage. He remarked that rabbits mate during pregnancy or pseudopregnancy but that they never ovulate after these matings, and he suggested that this circumstance arises because the functional corpus luteum secretes progestin, which prevents the discharge of the gonadotropic content of the pituitary body.

Bunster and Meyer¹²⁷ studied the effect of estrogen on the gonad-stimulating hormone of the anterior lobe of the pituitary body of castrated immature male and female rats in parabiosis with immature females. The data indicate that in the pituitary body of the castrated male rat a moderately higher gonad-stimulating activity develops than in that of the female rat. There is no qualitative difference in the sensitivity of the pituitary body of the two sexes to estrogen, the difference is quantitative only.

Lauson, Golden and Elmer Sevringhaus¹²⁸ observed the rate of increase in hypophysial gonadotropic content following ovariectomy in the rat, with observations on the weight of the hypophysis. They found that the increase in pituitary gonadotropic potency varied directly with the time that had elapsed since the animal was castrated.

Hamilton and Wolfe¹²⁹ injected synthetic androgenic substance (testosterone propionate) into rats and assayed the pituitary body for gonadotropic potency. They found that a marked lessening of gonadotropic potency resulted from the injection of androgen. The increase in gonadotropic capacity subsequent to castration (an increase which is augmented by the elapse of postcastration time) is largely, but not completely, negated by injection of androgen.

Chen and Van Dyke¹³⁰ studied the gonadotropic action of extract of the anterior lobe of the pituitary body after tryptic digestion and concluded that it abolished most of the luteinizing action of the majority

126 Makepeace, A. W. The Effect of Progestin upon the Anterior Pituitary, *Am J Obst & Gynec* **37** 457-459 (March) 1939.

127 Bunster, E., and Meyer, R. K. The Effect of Estrin on the Gonad-Stimulating Complex of the Anterior Pituitary of Parabiotic Rats, *Endocrinology* **23** 496-500 (Oct) 1938.

128 Lauson, H. D., Golden, J. B., and Sevringhaus, E. L. The Rate of Increase in Hypophyseal Gonadotropic Content Following Ovariectomy in the Rat, with Observations on Gland Weights, *Endocrinology* **25** 47-51 (July) 1939.

129 Hamilton, J. B., and Wolfe, J. M. The Effect of Synthetic Androgen upon the Gonadotropic Potency of the Anterior Pituitary, *Endocrinology* **22** 360-365 (March) 1938.

130 Chen, G., and Van Dyke, H. B. Gonadotropic Action of Anterior Pituitary Extract After Tryptic Digestion, *Proc Soc Exper Biol & Med* **40** 172-176 (Feb) 1939.

of the extracts McShan and Meyer¹³¹ expressed complete agreement with this observation They studied the effect of extracts of both trypsin and ptyalin on the gonadotropic activity of pituitary extract and found, they said, that

The luteinizing activity of extracts was largely, if not entirely, destroyed by trypsin, while it was relatively resistant to the action of the ptyalin preparations On the other hand the follicle-stimulating activity was resistant to trypsin, while it was destroyed by the ptyalin preparations

Abramowitz and Hisaw¹³² reported that crystalline trypsin maintained at p_H 7.1 completely destroys follicle-stimulating hormones, luteinizing hormones and the urinary hormones of pregnancy Breneman¹³³ reported augmentation of the pituitary gonadotropic hormone by chlorophyll, plant growth hormones and hemin Friedman¹³⁴ reported extraction of the gonadotropic hormone from the leaves of young oat plants

Friedman and Friedman¹³⁵ confirmed the results of R. T. Hill in finding the gonadotropic content of the pituitary body in the rabbit to be rapidly depleted within twenty-four hours after mating and in noting that restitution of the hormonal content of the pituitary body follows a characteristic curve during pseudopregnancy They found the hormone content to be highest in the early spring and lowest in the early winter Makepeace, Weinstein and Friedman¹³⁶ have confirmed this observation Wells¹³⁷ has studied the fluctuation in the gonadotropic potency of 71 male ground squirrels This potency varied markedly with the season and reached its highest point during the rutting period Werner¹³⁸ has

131 McShan, W. H., and Meyer, R. K. The Effect of Trypsin and Ptylin Preparations on the Gonadotropic Activity of Pituitary Extracts, *J. Biol. Chem.* **126** 361-365 (Nov.) 1938

132 Abramowitz, A. A., and Hisaw, F. L. The Effects of Proteolytic Enzymes on Purified Gonadotropic Hormones, *Endocrinology* **25** 633-637 (Oct.) 1939

133 Breneman, W. R. Augmentation of Pituitary Gonadotropic Hormone by Chlorophyll, Plant Growth Hormones and Hemin, *Endocrinology* **24** 488-493 (April) 1939

134 Friedman, M. H. Gonadotropic Extracts from the Leaves of Young Oat Plants, *Proc. Soc. Exper. Biol. & Med.* **37** 645-646 (Jan.) 1938

135 Friedman, M. H., and Friedman, G. S. Seasonal Variations in the Gonadotropic Hormone Content of the Rabbit Pituitary, *Endocrinology* **24** 626-630 (May) 1939

136 Makepeace, A. W., Weinstein, G. L., and Friedman, M. H. Effect of Coitus on Gonadotropic Content of Pituitary Glands of Pseudopregnant Rabbits, *Endocrinology* **22** 667-668 (June) 1938

137 Wells, L. J. Gonadotropic Potency of the Hypophysis in a Wild Male Rodent with Annual Rut, *Endocrinology* **22** 588-594 (May) 1938

138 Werner, S. C. Failure of Gonadotropic Function of the Rat Hypophysis During Chronic Inanition, *Proc. Soc. Exper. Biol. & Med.* **41** 101-105 (May) 1939

noted the failure of the gonadotropic function of the hypophysis in the rat during chronic inanition. He called attention to the similar findings which occur in human beings in such conditions as anorexia nervosa and marked loss in weight.

Fevold and Fiske¹³⁹ studied inhibition of the action of the follicle-stimulating hormone by the pituitary body. They were unable to separate this antagonistic principle from the luteinizing hormone. The authors concluded that the inhibiting agent is either the luteinizing hormone or a factor closely associated with and similar to it.

Foster and Fevold¹⁴⁰ discussed the relation of the two gonadotropic hormones in juvenile rabbits. The discussion regarding the number of gonadotropic hormones has continued. Saunders and Cole¹⁴¹ stated

It is concluded from these experiments that, whereas it is possible to obtain from pituitary two gonadotropic extracts, having somewhat different effects, it is not certain that these are due to two separate hormones. Whether the ovarian response shall be follicle-stimulation or luteinization seems to depend to at least as great an extent on the manner of injection and state of the ovary as on the type of extract used. A new hypothesis is suggested as an alternative for the two-hormone theory.

Fevold¹⁴² presented his evidence for concluding that the follicle-stimulating and the luteinizing hormone are separate.

Goss and Cole¹⁴³ have outlined their methods for the purification of the gonadotropic hormone of mares, which is by far the most potent hormone of this type yet available and the one which is being given an extensive clinical trial.

Jensen and associates¹⁴⁴ and Evans and co-workers¹⁴⁵ reported their conclusion that one of the gonadotropic hormones should be listed

139 Fevold, H. L., and Fiske, V. M. The Inhibition of the Action of the Follicle Stimulating Hormone by the Pituitary, *Endocrinology* **24** 823-828 (June) 1939.

140 Foster, M. A., and Fevold, H. L. The Interrelationship of the Pituitary Gonadotropic Hormones in Follicular Development and Ovulation of the Juvenile Rabbit, *Am J Physiol* **121** 625-632 (March) 1938.

141 Saunders, F. J., and Cole, H. H. On the Reliability of Present Methods for Characterizing Two Gonadotropic Hormones, Follicle-Stimulator and Luteinizer, *Endocrinology* **23** 302-317 (Sept.) 1938.

142 Fevold, H. L. Extraction and Standardization of Pituitary Follicle-Stimulating and Luteinizing Hormones, *Endocrinology* **24** 435-446 (April) 1939, Chemical Differences of Follicle-Stimulating and Luteinizing Hormones of Pituitary, *J Biol Chem* **128** 83-92 (April) 1939.

143 Goss, H., and Cole, H. H. Further Studies on the Purification of Mare Gonadotropic Hormone, *Endocrinology* **26** 244-249 (Feb) 1940.

144 Jensen, H., Simpson, M. E., Tolksdorf, S., and Evans, H. M. Chemical Fractionation of the Gonadotropic Factors Present in Sheep Pituitary, *Endocrinology* **25** 57-62 (July) 1939.

145 Evans, H. M., Simpson, M. E., Tolksdorf, S., and Jensen, H. Biological Studies of the Gonadotropic Principles in Sheep Pituitary Substance, *Endocrinology* **25** 529-546 (Oct.) 1939.

as an "interstitial-cell stimulating hormone" The validity of this conclusion has not been confirmed

Fluhmann ¹⁴⁶ listed his evidence to justify the classification of gonadotropic substances into three groups anterior pituitary, chorionic and equine gonadotropic hormones

Greep ¹⁴⁷ has studied the effect of gonadotropic hormones on the persisting corpora lutea in hypophysectomized rats He utilized such rats to determine the cause of the persistence of corpora lutea, which, although nonfunctional, are at least morphologically wholly normal The only substance which by itself will induce histologic involution has, paradoxically, been found to be luteinizing hormone, the same substance which under proper conditions acts as a stimulus for the formation of the corpora lutea It is difficult at present to fit this observation into the current conceptions of the physiologic processes occurring in the normal reproductive cycle Greep observed that when both follicle-stimulating and luteinizing hormones were administered simultaneously involution of the persistent corpora was remarkably rapid

Bunde ¹⁴⁸ injected certain gonadal and gonadotropic hormones into rats and observed their effects on the gestation period Follicle-stimulating and luteinizing hormones injected during the latter part of pregnancy inhibited parturition The fetuses were carried normally to term or beyond and in some instances were abnormally large Unfractionated pituitary extract reacted in essentially the same way The serum of pregnant mares was less effective in inhibiting parturition Progesterin had no inhibiting effect

Friedgood ¹⁴⁹ induced estrogenic behavior in anestrus rats with follicle-stimulating and luteinizing hormones of the anterior lobe of the pituitary body

Foster ¹⁵⁰ commented on the different response which is obtained by the injection of varying combinations of pituitary gonadotropic hormones into rabbits of different ages and in various physiologic states

146 Fluhmann, C F Comparative Studies of Gonadotropic Hormones, *Endocrinology* **25** 193-198 (Aug) 1939

147 Greep, R O The Effect of Gonadotropic Hormones on the Persisting Corpora Lutea in Hypophysectomized Rats, *Endocrinology* **23** 154-163 (Aug) 1938

148 Bunde, C A The Effects of Certain Gonadal and Gonadotropic Hormones on the Gestation Period of the Rat, *Endocrinology* **23** 345-352 (Sept) 1938

149 Friedgood, H B Induction of Estrous Behavior in Anestrous Cats with the Follicle-Stimulating and Luteinizing Hormones of the Anterior Pituitary Gland, *Am J Physiol* **126** 229-233 (June) 1939

150 Foster, M A The Differential Action of Pituitary Gonadotropic Hormones upon the Secretory Capacity of the Graafian Follicle and Corpus Luteum, *Am J Physiol* **121** 633-639 (March) 1938

Robson¹⁵¹ reported on the role of the gonadotropic hormones in the maintenance of luteal function. Results of his experiments suggest that in normal rats the anterior lobe of the pituitary body maintains luteal function not by the direct action of gonadotropic hormones on the corpus luteum but by stimulating the ovaries to secrete estrin, which in its turn acts on the corpus luteum. His work led him to pose the question of whether it is necessary to postulate the presence of the luteinizing hormone, since, according to his conclusion, luteal function is controlled by estrogen and the gonadotropic hormone has no direct action on the corpus luteum.

Hisaw, Fevold and Greep¹⁵² have reviewed material on the gonadotropic hormones and described the effect of the follicle-stimulating hormone on the ovary, the different actions of the luteinizing hormone, the augmentation achieved when both are administered and the effects produced in the male.

Engle¹⁵³ has published an important review article on the gonadotropic substances of the blood, the urine and other body fluids.

Various methods of assaying gonadotropic hormones have been described. Friedman¹⁵⁴ concluded that the best test animal is the post-partum rabbit. D'Amour¹⁵⁵ considered the ovarian weight method preferable to that based on the formation of corpora lutea. Collip¹⁵⁶ has published a report on the third international conference at Geneva which was to set international standards of pregnancy urine gonadotropin, mares' serum gonadotropin and certain hormones of the anterior lobe of the pituitary body. He stated

Although as yet only the standard of chorionic gonadotrophin is available, the writer has been informed that the standard for gonadotrophin of pregnant mares' serum will be ready for distribution within a few weeks, and that for prolactin shortly thereafter. It is to be hoped that as these standards become available all workers will avail themselves of them.

151 Robson, J. M. The Rôle of Gonadotropic Hormone in the Maintenance of Luteal Function, *Quart J Exper Physiol* **28** 49-59 (June) 1938.

152 Hisaw, F. L., Fevold, H. L., and Greep, R. O. The Pituitary Gonadotropic Hormones, *A Research Nerv & Ment Dis, Proc* (1936) **17** 247-256, 1938.

153 Engle, E. T. Gonadotrope Stoffe in Blut, Harn und in anderen Körperflüssigkeiten, *Arch f Gynak* **166** 131-167, 1938.

154 Friedman, M. H. The Assay of Gonadotropic Extracts in the Post-partum Rabbit, *Endocrinology* **24** 617-625 (May) 1939.

155 D'Amour, M. C., and D'Amour, F. E. The Assay of Gonad Stimulating Preparations, *J Pharmacol & Exper Therap* **62** 263-283 (March) 1938.

156 Collip, J. B. International Standards for Pregnancy Urine Gonadotrophin, Mares' Serum Gonadotrophin and Certain Anterior Pituitary Hormones, *Endocrinology* **25** 318-324 (Aug) 1939.

Frank and Berman¹⁵⁷ compared the four methods of bioassay for the gonadotropic factors and concluded that none of them can be considered better than roughly quantitative. They wrote as follows:

A complete bioassay of the gonadotropic factors necessitates (a) a concentration method which precipitates both follicle stimulating and luteinizing factors (acetone, acid alcohol methods), (b) ovarian 'values'. The following is suggested as the units: (a) the smallest amount of material which produces the full growth of 6 follicles, (b) the smallest amount of material which produces contiguous corpora lutea.

Comparing the relative merits and disadvantages of these several procedures, we have decided to continue to use the ovarian values as our method for bioassay, because it appears to present a more comprehensive picture of the gonadotropic forces at work. We realize, however, that a more extensive statistical investigation of this problem is required in order to justify this choice for general adoption.

Rubenstein and Abarbanel¹⁵⁸ studied the effect of extracts of the anterior lobe of the pituitary body on spermatogenesis in rats and found that in normal immature male rats there was a premature descent of the testes with increased proliferative activity of the germ cell layer. The sperm cells showed no evidence of hastened maturation. Interstitial tissue was increased, and there was a precocious development of the epididymis to adult proportions. Injection of extracts of the anterior lobe of the pituitary body into normal mature rats caused a definite increase in the weight of the testes, moderate increase in the proliferation of the germinal epithelium and a moderate increase in tubular diameter.

Hoffman and Fouch¹⁵⁹ used a cutaneous test as an aid in the diagnosis of pregnancy. These results were not sufficiently reliable to secure acceptance of the method as a biologic test.

Page¹⁶⁰ did not find a markedly toxic substance in the blood of eclamptic patients, nor did he observe any evidence of hypersecretion of the posterior lobe of the pituitary body.

Greene¹⁶¹ was able to induce in rabbits a disorder resembling the toxemia of pregnancy by the injection of an aqueous extract of the pituitary body of apes into rabbits at the twenty-seventh day of gestation.

157 Frank, R. T., and Berman, R. L. A Comparison of Four Methods of Bioassay for the Gonadotropic Factors, *Endocrinology* **25** 683-688 (Nov.) 1939.

158 Rubenstein, H. S., and Abarbanel, A. R. Effect of Anterior Pituitary Extract on Spermatogenesis in Rat, *J. Urol.* **41** 773-779 (May) 1939.

159 Hoffman, P. E., and Fouch, F. L. Results of Skin Tests for Pregnancy, *Am. J. Obst. & Gynec.* **35** 680-682 (April) 1938.

160 Page, E. W. Effect of Eclamptic Blood upon Urinary Output and Blood Pressure of Human Recipients, *J. Clin. Investigation* **17** 207-218 (May) 1938.

161 Greene, H. S. N. Experimental Induction of a Disorder Resembling Toxemia of Pregnancy in the Rabbit, *Proc. Soc. Exper. Biol. & Med.* **40** 606-608 (April) 1939.

D'Amour¹⁶² reported qualitative studies of normal gonadotropic substances in the urine of normal women. He reported marked fluctuations in the hormonal content, depending on the stage of the menstrual cycle. He sought to determine how the gonadotropic substances in the urine of normal women were related to the menstrual cycle, and he compared the gonadotropin from the urine of normal menstruating women with the gonadotropic hormones of the anterior lobe of the pituitary body, of pregnancy urine, of menopausal urine and of pregnant mares' serum. On the basis of his and other observations he decided that the following could be used as a working hypothesis: The anterior lobe of the pituitary body stimulates and produces follicle-stimulating hormone, this maintains the normal growth of follicles, the follicles ripen and produce estrogen, estrogen acts on the anterior lobe of the pituitary body, causing production of the luteinizing hormone, and a combination of luteinizing hormone and follicle-stimulating hormone causes ovulation.

Fluhmann and Murphy¹⁶³ studied the content of the estrogenic and gonadotropic hormones of the blood of women at the climacteric and of castrated women and attempted to determine the possible relation of these hormones to the production and alleviation of symptoms associated with the cessation of ovarian function. They found that failing or absence of ovarian function is not associated with complete disappearance of substances having estrogenic properties when injected into spayed rodents. The hormone may be detected at cyclic intervals or it may be constant, but no relation between climacteric symptoms and absence or presence of the hormone could be established. A gonadotropic substance, probably originating in the anterior lobe of the pituitary gland, was found in excessive amounts in the blood of the female of climacteric age and after castration, it bears a distinct relation to the severity of the so-called climacteric symptoms.

Ascheim, Portes and Mayer¹⁶⁴ discussed the treatment with gonadotropic hormone of a variety of conditions, including hypophysial cachexia, amenorrhea, sterility, hemorrhagic syndromes, symptoms of hypophysial hyperfunction and others. This article is subject to the same criticism which can be leveled at others of its type—oversimplification of a complex subject and unjustified assumption that endocrinologic knowledge has reached the point at which physicians can intelligently prescribe for unintelligible situations.

162 D'Amour, F. E. A Qualitative Study of Normal Gonadotropin, *Am J Physiol* **127** 649-653 (Nov) 1939

163 Fluhmann, C. F., and Murphy, K. M. Estrogenic and Gonadotropic Hormones in Blood of Climacteric Women and Castrates, *Am J Obst & Gynec* **38** 778-785 (Nov) 1939

164 Ascheim, S., Portes, L., and Mayer, M. L'hormonothérapie hypophysaire gonadotrope, *Ann d'endocrinol* **1** 164-178 (May) 1939

Johnston and Maroney ¹⁶⁵ studied the nitrogen and calcium balances as affected by extracts containing growth and gonadotropic hormones administered for short periods to growing children. They wrote

A variety of responses followed—anabolic, katabolic and negative—which might be explained as being conditioned by *a*, the presence or absence of a hormonal defect, *b*, the state of the stores as judged by the control balance and *c*, the age of the child. Subjects included several girls with menstrual difficulties at puberty, 4 dwarfs—a cretin, an achondroplastic and 2 ateleotics, and a number of children who apparently had no endocrine abnormalities. Instances of complete loss of response in the nature of antihormone effect were encountered.

Boycott and Smiles ¹⁶⁶ called attention to the fact that the diagnosis of hydatid mole by biologic assay of gonadotropic hormone alone is not reliable.

Grace ¹⁶⁷ recorded the fallibility of the excretion of the follicle-stimulating gonadotropic hormone (prolan A) as a prognostic agent in instances of teratoma testis.

Moppett ¹⁶⁸ reported that gonadotropic extracts of the anterior lobe of the pituitary body and extracts of growth hormone appeared to stimulate the growth of tumors in mice.

Turner ¹⁶⁹ reported his results in the treatment of cryptorchidism with hormones of the anterior lobe of the pituitary body and similar hormones. He obtained descent in 14 of 26 cases, partial descent in 8 and failure in 4. The average length of treatment was twenty-five weeks, the average total dose was 13,000 rat units. There were no serious complications, but 1 boy had precocious secondary sexual development and another had softening of the testes after they had descended. Turner thought that treatment should be administered before the eighth year of the patient.

Dorff ¹⁷⁰ reported on 12 boys with intra-abdominal cryptorchidism who were treated with gonadotropic substances. In 9 of these, the testes

165 Johnston, J. A., and Maroney, J. W. Observations on Nitrogen and Calcium Balances as Affected by Growth and Gonadotropic Hormones Administered for Short Periods to Growing Children, *Endocrinology* **25** 199-210 (Aug.) 1939.

166 Boycott, M., and Smiles, J. M. Diagnosis of Hydatidiform Mole by Biological Assay, *Lancet* **1** 1428-1430 (June 24) 1939.

167 Grace, E. J. Fallibility of Prolan A Excretion as Prognostic Agent in Cases of Teratoma Testis, *Am. J. Surg.* **45** 280-281 (Aug.) 1939.

168 Moppett, W. Substances Controlling the Growth of Implanted Tumours, *M. J. Australia* **2** 1065-1069 (Dec. 18) 1937.

169 Turner, H. H. Anterior Pituitary Gonadotropic and Anterior Pituitary-Like Hormones in the Treatment of Cryptorchidism, *South. M. J.* **31** 381-387 (April) 1938.

170 Dorff, G. B. Intra-Abdominal Cryptorchidism Treated with Gonadotropic Substance. Observations in a Series of Twelve Prepuberal Boys, *I. A. M. A.* **110** 1799-1802 (May 28) 1938.

descended to the inguinal canal Doiff used the gonadotropic hormone of the urine of pregnant women In 3 patients the testes came into the scrotum

Bigler, Hardy and Scott¹⁷¹ reviewed the literature and found the records of 191 patients who had been treated with the gonadotropic substances of the urine of pregnant women Of these patients, 101 (52.8 per cent) were obese and 90 (47.2 per cent) had what is described as "a normal build" In 167 cases there was complete scrotal descent

Bigler, Hardy and Scott¹⁷² concluded that the best surgical repair of cryptorchidism followed preoperative treatment with gonadotropic substance from the urine of pregnant women (antuitrin-S) Postoperative treatment produced no beneficial effects The best results were obtained when the boys were between 7 and 10 years of age

Heckel¹⁷³ has published an excellent article on the treatment of sterility with gonadotropic and gonadotropic-like factors He pointed out the many difficulties in the attempt to define the problems involved in any given case and the greater difficulties in the attempt to treat this condition He reported that in some instances both gonadotropic principles and the extract of pregnancy urine appear to influence the number and viability of the spermatozoa, but that in some patients the phenomena are only temporary Heckel's figures on the induction of fertility were lower than those which other authors have reported He called attention to the difficulty of determining just how much relation there is between the various endocrine glands and spermatogenesis

Kunstadter¹⁷⁴ attempted to treat hypogonadism in the male patient with serum of pregnant mares He stated the following conclusion

It is believed that mares' serum is of definite value in the treatment of certain cases of hypogonadism and cryptorchidism

As yet the optimal effective dose has not been established, but we believe that 50 to 100 U intramuscularly 3 times weekly probably will be more effective than the 10 to 20 U intramuscularly 3 times weekly administered to our patients With the higher dosage results would probably be obtained in a shorter period of time

171 Bigler, J. A., Hardy, L. M., and Scott, H. V. Gonadotropic Principles in the Treatment of Cryptorchidism. A Review of the Literature, *Am J Dis Child* **55** 100-111 (Jan) 1938

172 Bigler, J. A., Hardy, L. M., and Scott, H. V. Cryptorchidism Treated with Gonadotropic Preparations. III. Surgical Repair of Cryptorchidism With and Without Gonadotropic Therapy, *Am J Dis Child* **56** 989-996 (Nov) 1938

173 Heckel, N. J. The Gonadotropic and the Gonadotropic-Like Factor in the Treatment of Male Sterility, *Endocrinology* **22** 111-114 (Jan) 1938

174 Kunstadter, R. H. The Treatment of Hypogonadism in the Male with the Gonadotropic Principle of Pregnant Mares' Serum, *Endocrinology* **25** 661-669 (Nov) 1939

From a clinical standpoint there is also great difference of opinion Israel,¹⁷⁵ in concluding his article, stated

The treatment of dysfunctional menstrual disorders should be directed toward the primary site, usually the anterior hypophysis or the ovaries, of the derangement. Several therapeutic measures, each for a different purpose, may be required to reconstitute normal menstruation.

Certain basic principles of organotherapy must be known before any of the currently employed therapeutic agents may be applied in an aberration of the menstrual function.

This concept is not shared by all workers in this field.

Fluhmann¹⁷⁶ carefully studied 19 patients who had dysmenorrhea. A series of 85 tests was conducted on these patients, and in 18 instances, the results failed to show any variation from the normal.

Sevringhaus¹⁷⁷ has discussed the treatment of menstrual disturbances, describing certain conditions in which, he said, he felt either ovarian or pituitary treatment offered advantages. He emphasized present difficulties of diagnosis and greater difficulties in treatment.

Hamblen¹⁷⁸ reported that a consideration of the results obtained in the treatment of anovulatory menometrorrhagia of functional character by gonadotropic principles seems to indicate that these principles have no claims for specificity and that symptomatic, ovarian or endometrium responses do not warrant the employment of those factors. Since the histologic aspects of functional amenorrhea of anovulatory type and those of so-called endocrine sterility are the same, similar assumptions seemed justified in these two instances. Hamblen¹⁷⁹ in a later article reviewed the literature and pointed out the various difficulties inherent in attempts to evaluate clinically ovarian responses to gonadotropic therapy. "Consideration of the clinical data available," he wrote, "indicates that there exists little definite proof that therapeutic efficiency has been established for the gonadotropes in most supposed endocrinopathic gynecology."

175 Israel, S. L. The Treatment of Dysfunctional Menstrual Disorders, *Endocrinology* **22** 253-261 (Feb.) 1938.

176 Fluhmann, C. F. Endocrine Theories of Dysmenorrhea, *Endocrinology* **23** 393-397 (Oct.) 1938.

177 Sevringhaus, E. L. The Choice of Ovarian or Pituitary Therapy for Menstrual Disturbances, *Ann. Int. Med.* **13** 629-635 (Oct.) 1939.

178 Hamblen, E. C. Observations on the Clinical Employment of Pituitary and Pituitary-Like Gonadotropic Principles in Certain Conditions Characterized by Failure of Ovulation, *Am. J. Surg.* **41** 35-38 (July) 1938.

179 Hamblen, E. C. The Clinical Evaluation of Ovarian Responses to Gonadotropic Therapy, *Endocrinology* **24** 848-865 (June) 1939.

Kobak¹⁸⁰ called attention to the danger of physicians' relying too much on the results of a laboratory test. He reported a case in which a woman had expelled a hydatid mole. Reactions to subsequent Friedman tests were positive, and it was assumed that the large uterus represented a recurrence of the mole. Abdominal hysterectomy was performed. The uterus was found to contain a normal fetus and placenta.

Schaefer, Sharp and Lammy¹⁸¹ discussed in detail the use of gonadotropic substance from the urine of pregnant women in the treatment of 16 patients who had genital hypoplasia and cryptorchidism, 15 who had amenorrhea and 13 who had menometrorrhagia.

Schteingart¹⁸² reported abnormalities of genital function and development among 70 per cent of sterile women. He listed the conditions as follows: (1) moderate genital hypoplasia to true infantilism in 80 per cent of the sterile women, (2) menstrual disturbances and amenorrhea in 40 per cent, (3) alterations of the sella turcica in 80 per cent, (4) obesity in 60 per cent, and (5) two disorders, (a) moderately lowered basal metabolism in many cases (but not characteristic) and (b) almost constantly lowered specific dynamic action. He also mentioned other less constant symptoms, such as deviations of stature and anomalies of the hair, including abnormal distribution, discrete hypotrichosis and advanced hirsutism.

Watson, Smith and Kurzrok¹⁸³ studied the relation of the menopause to gonadotropic hormones and concluded that the event is referable to a loss of response of the ovaries to gonadotropic hormones.

Campbell and Sevringhaus¹⁸⁴ said that hypofunction of the pituitary gland is responsible for amenorrhea, oligomenorrhea, menorrhagia, irregular cycles and sterility with anovulatory bleeding, and that these conditions are caused by a deficiency of the gonadotropic hormones and abnormalities in the timing of the liberation of these hormones. They concluded that in many instances polycystic ovaries are caused by long-continued stimulation of the pituitary body. For accurate diagnosis and conduct of treatment they advised endometrial biopsy, studies of vaginal epithelium and determinations of pregnandiol.

180 Kobak, A. J. The Interpretation of Excessive Gonadotropic Hormones Excreted in the Urine in Early Pregnancy, *J. A. M. A.* **110** 1179-1180 (April 9) 1938.

181 Schaefer, R. L., Sharp, E. A., and Lammy, J. V. Clinical Indications for Anterior Pituitary-Like Sex Hormone, *Endocrinology* **22** 643-662 (June) 1938.

182 Schteingart, M. El factor hipofisario en la esterilidad, *Prensa medica argent.* **25** 901-905 (May 11) 1938.

183 Watson, B. P., Smith, P. E., and Kurzrok, R. Relation of Pituitary Gland to Menopause, *Am. J. Obst. & Gynec.* **36** 562-570 (Oct.) 1938.

184 Campbell, R. E., and Sevringhaus, E. L. Pituitary Gonadotropic Extracts for the Treatment of Amenorrhea, Menorrhagia and Sterility, *Am. J. Obst. & Gynec.* **37** 913-928 (June) 1939.

Murphy and Fluhmann¹⁸⁵ studied the relation of estrogenic and gonadotropic hormones to climacteric symptoms. They stated

The onset of the climacteric period is not associated with the disappearance of estrogen from the circulating blood

There is a relationship between the onset and severity of vasomotor symptoms and the presence of increased gonadotropic hormone in the blood Albright, Frank et al, and others have shown that with the administration of large doses of estrogen an amelioration of symptoms occurs and the hormone disappears from the urine

Fluhmann¹⁸⁶ has discussed the biologic differences between sex hormones of the anterior lobe of the pituitary body and gonadotropic substances from the urine of pregnant women. He obtained discouraging results in the treatment of amenorrhea with pituitary gonadotropic hormones and called attention to the use of the hormone of the urine of pregnant women for patients having profuse uterine hemorrhages with hyperplasia of the endometrium as well as for patients with undescended testes

Summary—Van Dyke¹⁸⁷ stated

If the number of articles published were acceptable as a safe basis of judgment, it could easily be concluded that the gonadotropic hormones are the most important secreted by the anterior pituitary. This field of inquiry is attractive not only because of its inherent importance but also because the probability of securing fruitful results is great. There can be no doubt that the anterior pituitary secretes gonadotropic hormone(s) essential for the normal functioning of the gonads of mammals and other vertebrates. As a result, nearly every investigator interested in the physiology of the gonads has quickly entered or wandered into the rich and diversified field of pituitary-gonad interrelationships—sometimes without realizing he is there. Furthermore, work may be greatly facilitated by the fact that the assay of the hormones with a fair degree of accuracy is often, but not always, easily accomplished.

Despite all the labor represented by a vast number of reports during the past few years, it is not yet possible to enumerate satisfactorily the gonadotropic hormones of the pituitary. Separate follicle-stimulating and luteinizing hormones are generally believed to exist, it is by no means certain that the former specifically maintains the mammalian seminiferous tubules, whereas the latter insures the normal secretion of testicular hormone by the interstitial cells. It has been reported that principles synergizing with or antagonizing gonadotropic hormone have been extracted from the pituitary, however, their physiological importance is largely postulated from deduction. Several authors have recognized the great importance

185 Murphy, K. M., and Fluhmann, C. F. The Relation of Estrogenic and Gonadotropic Hormones to Climacteric Symptoms, *West J Surg* **46** 451-454 (Sept.) 1938

186 Fluhmann, C. F. Biologic Differences Between Anterior Pituitary Sex Hormone and Gonadotropic Substances from Pregnant Women, *A Research Nerv & Ment Dis, Proc* (1936) **17** 350-360, 1938

187 Van Dyke, H. B. The Physiology and Pharmacology of the Pituitary Body, Chicago, University of Chicago Press, 1938, vol 2, pp 47-48

of excluding the animal's own pituitary in determining accurately qualitative and quantitative effects of extracts. The increased accuracy of interpretation more than justifies the great increase of labor required. Final judgment on the effect(s) of an extract should be based upon experiments with hypophysectomized animals.

The follicle-stimulating hormone often excreted in human urine in considerable amounts after spaying or castration or after the menopause probably originates in the anterior pituitary. On the other hand, the gonadotropic substances discussed in chapter iv appear not to be secreted by the hypophysis. These substances are prolactin (from the chorionic cells of the human pregnant uterus), the gonadotropic hormone characteristic of pregnant-mare serum (likewise probably secreted by chorionic or endometrial cells), and the gonadotropic hormones of neoplasms such as hydatidiform mole, chorionepithelioma, and testicular tumor (from the cells of the neoplasms).

ANTIHORMONES

A. E. Severinghaus and Thompson¹⁸⁸ made a cytologic study of the hypophyses of 2 dogs and 2 sheep which had received prolonged injections of extracts of the pituitary glands of sheep, and of 2 dogs into which anti-hormone serum had been injected. They wrote:

The most important of the findings may be enumerated as follows: (1) The "Crooke changes" heretofore described only in the human pituitary gland have been experimentally produced in dogs, most prominently in the hypophyses of the dogs injected with the canine antihormone. (2) The changes in basophiles characteristic of both castration and thyroidectomy were observed in the hypophyses of the long-time injected dogs. (3) The presence of basophilic granules in the perivascular spaces and in the capillaries has been observed.

It is possible that the following reactions occurred in sequence during the course of prolonged injections of the sheep-pituitary extract: (1) An initial activation of the endocrine glands subsidiary to the pituitary gland occurred. In the sheep this process continued for the entire 6 months of injections. (2) The increased secretion of the subsidiary glands in turn activated the hypophyseal function. (3) The foreign protein linked to the injected sheep-extract gradually produced in the dogs a tissue and humoral resistance (antihormones), which ultimately inactivated the sheep-extract as well as certain pituitary hormones of the injected animal itself. (4) Thus, the antihormones produced a state of physiological hypophysectomy, which caused subsequent atrophy of the subsidiary glands. (5) The atrophy of the thyroid and gonads (and adrenals?) produced the final changes in the hypophyses characteristic of gonadectomy and thyroidectomy (and adrenalectomy?).

The Crooke changes characteristically found in the Cushing syndrome, associated with a diminished function of the gonads and thyroids, are believed to be related in some way to the effects of the inactivation of the subsidiary endocrine glands by the antihormone in these animals.^{188b}

188 Severinghaus, A. E., and Thompson, K. W. (a) Production of Antihormones by Prolonged Administration of Pituitary Extract. Effect on Anterior Hypophysis, *Proc. Soc. Exper. Biol. & Med.* **40**: 627-629 (April) 1939, (b) Cytological Changes Induced in Hypophysis by Prolonged Administration of Pituitary Extract, *Am. J. Path.* **15**: 391-412 (July) 1939.

Werner¹⁸⁹ injected a beef pituitary substance containing thyrotropic hormone into 11 guinea pigs and found that refractoriness developed in 10 of these. A flavianate preparation made from the hypophysis of the same species, on the other hand, produced stimulation in 21 of 26 guinea pigs.

Rowlands and Young¹⁹⁰ found that antiserum produced by the injection of a crude pyridine extract of the anterior lobe of the pituitary body of the ox exhibits much greater antithyrotropic activity than antiserum obtained by the injection of physiologically equivalent amounts of a relatively purified thyrotropic preparation. Antiprolactin serum obtained by the daily injection of relatively pure prolactin containing no detectable thyrotropic hormone possessed definite antithyrotropic potency. Precipitin reactions between antithyrotropic serum and thyrotropic preparations were not found to be specific for the pituitary antigen. This work was based on a previous study by Harington and Rowlands¹⁹¹.

Young¹⁹² studied the production of antiserum to prolactin containing the glycotropic (anti-insulin) factor of the anterior lobe of the pituitary body. The serum of animals so treated for twelve weeks or more showed marked ability to prevent the hypertrophic response of the crop gland of the pigeon to prolactin. Rabbits which had received daily injections of prolactin for eighteen weeks showed a normal hypoglycemic response to insulin after the administration of a potent pituitary glycotropic preparation, that is, they were insensitive to glycotropic action of the extract. Bischoff and Lyons¹⁹³ were able to neutralize the crop gland-stimulating effect of beef and sheep mammatropin by injection into the pigeons of antimammatropic serum prepared in rabbits against either beef or sheep mammatropin.

Dohan and Lukens¹⁹⁴ studied the effectiveness of antihormones in the treatment of pancreatic diabetes. Two completely depancreatized dogs which received intraperitoneal injections of serum from a dog treated for more than nine months with extract of the anterior lobe of

189 Werner, S. C. The Thyrotropic Hormone and the Antihormone Problem *Endocrinology* **22** 291-301 (March) 1938.

190 Rowlands, I. W., and Young, F. G. The Capacity of Pituitary Preparations Containing the Thyrotropic Hormone to Induce the Formation of Antisera, *J. Physiol.* **95** 410-419 (April) 1939.

191 Harington, C. R., and Rowlands, I. W. Fractionation of Antithyrotropic and Anti-Gonadotropic Sera, *Biochem. J.* **31** 2049-2054 (Nov.) 1937.

192 Young, F. G. The Production of Antisera to Preparations of Prolactin Containing the Glycotropic (Anti-Insulin) Factor of the Anterior Pituitary Gland, *Biochem. J.* **32** 656-664 (April) 1938.

193 Bischoff, H. W., and Lyons, W. R. Immunologic Investigation of Hypophyseal Mammatropic Preparations, *Endocrinology* **25** 17-27 (July) 1939.

194 Dohan, F. C., and Lukens, F. D. W. Antihormone Effects in Pancreatic Diabetes, *Proc. Soc. Exper. Biol. & Med.* **42** 167-171 (Oct.) 1939.

the pituitary body showed marked decrease in the amount of sugar in the urine. Two completely depancreatized dogs into which extract of the anterior lobe of the pituitary body was injected for thirty or more days showed after cessation of injections much less severe diabetes during fasting than had been present before injection. Metabolic behavior of these 4 dogs was much like that of depancreatized, hypophysectomized animals.

Zondek and associates¹⁹⁵ found that, according to their observations, the quantitative neutralization of "prolan" (the follicle-stimulating gonadotropic principle) and "antiprolan" follows strict laws, and they distinguished this reaction from fermentation reactions and from most of the immune reactions. Bunde and Hellbaum¹⁹⁶ studied the chemical and physical properties of gonadotropic antagonists.

Thompson¹⁹⁷ was able to interrupt the pregnancy of 12 dogs by the intravenous injection of a non-species-specific antigonadotropic canine serum. The action of the antiserum was comparable to that of physiologic hypophysectomy, and it may have been brought about by conferring on the dog a passive resistance (immunity) to its own pituitary gonadotropic hormone. Normal canine serum did not produce this effect. The antihormone did not cause any objective permanent ill effects in 3 dogs in which abortion had occurred, 2 of which later became pregnant and were again affected by abortion and 1 of which had a period of estrus. The aborted fetuses which were observed at delivery were alive, but subsequently died of prematurity and lack of maternal care. The antihormonal preparation used had no appreciable oxytocic activity when tested on the guinea pig uterus, it contained, however, a considerable amount of antidiuretic hormone, in addition to thyrotropic and gonadotropic antihormones. Kupperman and his associates¹⁹⁸ studied the effect of antigonadotropic serums on gonadotropic secretion in parabiotic rats. They reported

Anti-gonadotropic sera obtained from 2 adult, female rabbits receiving prolonged injections of an aqueous, supercentrifuged extract of sheep pituitary, inhibited the effectiveness of the endogenous gonadotropic secretion of the castrate partner's

195 Zondek, B., Sulman, F., and Hochmann, A. Relationship Between Inactivated Prolan and Antiprolan, *Proc Soc Exper Biol & Med* **39** 283-287 (Nov) 1938, The Antigonadotropic Factor. The Quantitative Aspects of the Prolan-Antiprolan Reaction, *ibid* **40** 96-98 (Jan) 1939.

196 Bunde, C. A., and Hellbaum, A. A. Some Chemical and Physiological Properties of the Gonadotropic Antagonist, *Am J Physiol* **125** 290-295 (Feb) 1939.

197 Thompson, K. W. The Termination of Pregnancy of Dogs by Gonadotropic Antihormone, *Endocrinology* **24** 613-616 (May) 1939.

198 Kupperman, H. S., Meyer, R. K., and Hertz, R. The Effect of Antigonadotropic Sera upon Gonadotropic Secretion in Parabiotic Rats, *Endocrinology* **24** 115-118 (Jan) 1939.

pituitary in 11 female-female and 7 female-male parabiotics when injected into either the castrated or intact partner. The inhibitory sera was of sufficient titer to prevent the ovarian hypertrophy and the extensive luteinization found in the control series.

Katzman and associates¹⁹⁹ reported on an entirely different observation, namely, on a study of a progonadotropic serum of animals treated with hypophyseal extracts. They found no evidence of antigonadotropic activity in the serums of sheep treated with chronic injection of extract of the pituitary body of sheep for as long as two hundred and sixty-two days. On the contrary, the serums continued to possess an enhancing action on the gonadotropic activity of this pituitary extract in immature female rats. The active factor of these serums also augments the action of rat pituitary extract, but not that of pig and beef pituitary bodies or that of the urine of pregnant and castrated women. When this factor is administered alone, it produces no apparent effect on the reproductive tracts of virgin female rabbits or of immature or mature female rats.

Dorff²⁰⁰ studied 19 boys who had been treated for genital underdevelopment with gonadotropic substance from the urine of pregnant women. The tests showed no evidence of any antihormone. The lag or apparent halt in development in some of the patients treated was overcome by increases in dose or by a change to a different commercial brand of the same principle.

Summary—The foregoing review emphasizes the unsettled state of knowledge regarding the question of the existence and entity of anti-hormones. Only one comment needs to be made. Until this question is settled, are clinicians justified in the extensive injection of pituitary hormones? Albright²⁰¹ is utilizing no anterior pituitary hormones in the treatment of patients in the Massachusetts General Hospital because of the possible harmful effects arising from the production of anti-hormones.

SIMMONDS' DISEASE

We consider Richardson's paper²⁰² to be one of the most important recent articles on the differential diagnosis of Simmonds' disease and anorexia nervosa. There have been reports of many cases of Simmonds' disease, most of which were really cases of anorexia nervosa. Richard-

199 Katzman, P. A., Wade, N. J., and Doisy, E. A. Progonadotropic Sera of Animals Treated with Hypophyseal Extracts, *Endocrinology* **25** 554-567 (Oct.) 1939.

200 Dorff, G. B. Antihormone Studies in Boys Treated with Anterior Pituitary-Like Hormone for Genital Underdevelopment, *Endocrinology* **22** 669-673 (June) 1938.

201 Albright, F. Personal communication to the authors.

202 Richardson, H. B. Simmonds' Disease and Anorexia Nervosa, *Arch. Int. Med.* **63** 1-28 (Jan.) 1939.

son has performed a valuable service in illustrating the striking changes which can be produced by simple inanition and the splendid recovery which follows the simple ingestion of adequate quantities of a balanced diet. The photograph accompanying his article should be remembered by those inclined to publish "before and after" photographs illustrating the startling cures resulting from hormonal therapy.

Lisser and Escamilla²⁰³ have published a critical statistical comparison of 69 verified and 134 unverified cases of Simmonds' disease. Their observations illustrate clearly the similarity of the findings in Simmonds' disease and those in anorexia nervosa. The fact that these authors could find only 69 verified cases of Simmonds' disease in the world literature again emphasizes the rarity of the condition.

Sheehan²⁰⁴ has published an excellent review of Simmonds' disease referable to postpartum necrosis of the anterior lobe of the pituitary body. He stated that ischemic necrosis of the anterior lobe of the pituitary body is found relatively frequently among women who die in the puerperium, occurring in more than 25 per cent of such women. It is caused by severe hemorrhage or collapse of the patient at the time of delivery and begins at the time of these complications. Sheehan described the changes which occur in a person who has suffered from this condition. During the puerperium there is complete absence of lactation and sometimes hypoglycemia is present. The uterus becomes superinvolved, the external genitals atrophy, menstruation does not return and libido is absent.

Hart and Lisa²⁰⁵ reported a case of Simmonds' disease in which the diagnosis was confirmed at necropsy. Osgood²⁰⁶ reported a case in which the same diagnosis was made and essentially the same findings were noted, but no explanation for this syndrome was discovered either during life or at necropsy. Dick and Dine²⁰⁷ discussed the use of pituitary extract in cases of Simmonds' disease, but acknowledged the possibility that any conclusions based on such treatment may be subject to error. Kunstadter²⁰⁸ discussed pituitary emaciation with improve-

203 Lisser, H., and Escamilla, R. F. Clinical Diagnosis of Simmonds' Disease (Hypophyseal Cachexia). Critical Statistical Comparison of Sixty-Nine Verified and One Hundred and Thirty-Four Unverified Cases, *Tr. A. Am. Physicians* **53** 210-220, 1938.

204 Sheehan, H. L. Simmonds' Disease Due to Post-Partum Necrosis of the Anterior Pituitary, *Quart. J. Med.* **8** 277-309 (Oct.) 1939.

205 Hart, J. F., and Lisa, J. R. Pituitary Cachexia. Report of a Case, *Endocrinology* **25** 130-133 (July) 1939.

206 Osgood, E. E. Pituitary Cachexia? *Endocrinology* **23** 656-660 (Nov.) 1938.

207 Dick, G. F., and Dine, W. C. Pituitary Extract in Simmonds's Disease, *Endocrinology* **22** 703-706 (June) 1938.

208 Kunstadter, R. H. Pituitary Emaciation, *Endocrinology* **22** 605-612 (May) 1938.

ment subsequent to endocrine therapy, but this report is subject to the same criticism mentioned by Dick and Dine. Bruckner and associates²⁰⁹ and Davis²¹⁰ have reported cases of anorexia nervosa in which the clinical picture of Simmonds' disease was present. Foley and associates²¹¹ reported an instance of tumor of the anterior lobe of the pituitary body associated with cachexia, hypoglycemia and duodenal ulcer. Brown and Eder,²¹² and Effkemann and Muller-Jager²¹³ reported the occurrence of Simmonds' disease following delivery. Seeger²¹⁴ reported a case in which a woman aged 62 died in shock shortly after appendectomy, for thirty years she had had the symptoms of Simmonds' disease and at necropsy was found to have marked atrophy of the anterior lobe of the pituitary body.

Straube's²¹⁵ report of the treatment of Simmonds' disease with extract of the posterior lobe of the pituitary body and adrenal cortical extract is open to doubt. This criticism applies also to Meyer's²¹⁶ treatment of Simmonds' disease by implantation of the pituitary body, Meyer reported dramatic improvement after the implantation of part of the pituitary body from a cat.

Bauer²¹⁷ has commented on the endocrine aspects of sprue and has emphasized the fact that many of the symptoms of this disease are similar to those reported on as associated with Simmonds' disease.

Summary—Simmonds' disease is rare. Most of the patients reported as having Simmonds' disease are really suffering from anorexia nervosa.

209 Bruckner, W. J., Wies, C. H., and Laviates, P. H. Anorexia Nervosa and Pituitary Cachexia, *Am J M Sc* **196** 663-673 (Nov) 1938.

210 Davis, H. P. Anorexia Nervosa. A Case Report, *Endocrinology* **25** 991-995 (Dec) 1939.

211 Foley, M. P., Snell, A. M., and Craig, W. McK. Anterior Pituitary Tumor Associated with Cachexia, Hypoglycemia, and Duodenal Ulcer, *Am J M Sc* **198** 1-8 (July) 1939.

212 Brown, C. E., and Eder, L. F. Acute Puerperal Hypophyseal Necrosis with Report of a Fatal Case, *Am J M Sc* **198** 166-171 (Aug) 1939.

213 Effkemann, G., and Muller-Jager, F. Ueber das Auftreten von Hypophysenvorderlappen-Insuffizienzen nach starken Post-partum-Blutungen, *Arch f Gynak* **168** 867-872, 1939.

214 Seeger, E. Akute hypophysare Insuffizienz nach Appendektomie, *Munchen med Wchnschr* **86** 882 (June 9) 1939.

215 Straube, G. Zur Therapie der Simmondsschen Krankheit, *Klin Wchnschr* **17** 1016-1017 (July 16) 1938.

216 Meyer, W. C. Untersuchungen und Beobachtungen an Fallen von hypophysarer Magersucht (Simmonds) und deren Behandlung, insbesondere durch Hypophysenimplantation, *Deutsches Arch f klin Med* **182** 351-358, 1938.

217 Bauer, J. Endocrine Aspects of Sprue. Their Relation to the Pituitary Syndrome in Anorexia Nervosa, *J Trop Med* **42** 245-250 (Aug 15) 1939.

CUSHING'S SYNDROME

Henderson ²¹⁸ has reviewed the surgical results in 336 cases in which the patients were operated on by Harvey Cushing. In these, 260 of the lesions were chromophobic tumors (including 32 mixed adenomas), 67 were tumors of the acidophilic cells and 11 were adenocarcinomas. There was no example of a basophilic adenoma in this series.

Eisenhardt and Thompson ²¹⁹ have reviewed the present status of so-called basophilism and have tabulated cases in which the diagnosis was verified. There have been 67 cases reported in the literature, with the incidence in sex approximately 2 females to 1 male. In 58 of these 67 cases (86 per cent) the tumor definitely was adenoma, and Eisenhardt and Thompson examined sections made in 39 of the 58 instances. In 33 the growth was true basophilic adenoma, in 2 it was chromophobic, in 2, mixed, in 1, a malignant tumor with metastasis, and in 1, unclassified. Excluded from consideration were the conglomerations of basophilic elements sometimes described as adenomas, but which so far as can be established have no clinical significance. The Crooke changes involving hyalinization of the cells were present in all these cases.

Maranon's ²²⁰ report showed that investigator's inclination to believe that the fundamental element in instances of Cushing's syndrome is hyperplasia of the adrenal glands. He stated that in many cases at the Pathologic Institute of Madrid basophilic adenomas have been found in instances of cardiac disease, renal disease, Parkinson's disease, cerebral hemorrhage and the like, without the least clinical sign of the presence of Cushing's syndrome. He reported 2 cases, in both of which not only the complete clinical picture of Cushing's syndrome but also tumors of the adrenal cortex were present, with no evidence of adenoma of the basophilic cells. Hall and his associates ²²¹ reported a case of Cushing's syndrome in which they found no endocrine tumor of any sort. Sections of the pituitary body did show the Crooke changes. Ecker ²²² studied the hyaline changes in the basophilic cells of the pituitary body obtained

218 Henderson, W. R. The Pituitary Adenomata. A Follow-Up Study of the Surgical Results in Three Hundred and Thirty-Eight Cases (Dr. Harvey Cushing Series), *Brit J Surg* **26** 811-921 (April) 1939.

219 Eisenhardt, L., and Thompson, K. W. A Brief Consideration of the Present Status of So-Called Pituitary Basophilism with a Tabulation of Verified Cases, *Yale J Biol & Med* **11** 507-522 (May) 1939.

220 Maranon, G. Sur la pathogenie du syndrome de Cushing, *Ann d'endocrinol* **1** 241-256 (July) 1939.

221 Hall, G., Kellett, C. E., and Stephenson, G. E. Cushing's Syndrome. Report of a Case in Which No Endocrine Tumor Was Found, *Lancet* **1** 862-865 (April 15) 1939.

222 Ecker, A. D. The Hyaline Change in the Basophil Cells of the Pituitary Body Not Associated with Basophilism, *Endocrinology* **23** 609-617 (Nov) 1938.

from patients not suffering from Cushing's syndrome. He studied the anterior lobe of the pituitary body in a series of 721 cases. In 54 of these there were small basophilic adenomas. The hyaline change was found to be present to a marked extent in 8 of the pituitary bodies, an incidence of 1.1 per cent. However, the clinical and postmortem records revealed no evidence of Cushing's syndrome, even though in 1 case a basophilic adenoma (the cells of which, however, presented no evidence of hyalinization) also was present. In his summary Ecker wrote:

The cells of the 54 basophil adenomas in this series, as well as of 18 others, representing a total of 72 adenomas previously found by Costello, were similarly examined. The hyaline change was present to a considerable degree in 4 cases (5.5 per cent). However, in these cases, there was neither hyalinization of the basophil cells outside of the adenomas nor any evidence of Cushing's syndrome in the clinical and post-mortem records. Finally, in none of the instances of hyalinization of the cytoplasm in the basophil cells in the 12 cases referred to were there such additional features as ballooning of the nucleus, excessive vacuolization, a tendency to multinucleation and general enlargement of the cells, which characterized the basophil cells of the pituitary body in 3 well-authenticated cases of pituitary basophilism which were used as controls. It appears, therefore, unwarranted to consider hyalinization or degranulation of the basophil cells in the anterior lobe of the pituitary body of the human as invariably associated with the state designated as pituitary basophilism. Whether the hyaline change, when found together with the other cytologic features mentioned, will prove to be the "alteration of fundamental significance in the causation of this syndrome" is an open question.

Anderson, Haymaker and Joseph²²³ have continued their hormonal and electrolytic studies of patients who have Cushing's syndrome. They concluded that patients with that syndrome have in their blood an excess amount of a substance which resembles the adrenal cortical hormone and which has the ability to prolong the life of adrenalectomized rats. This substance is secreted in significant amounts by the kidney. They published a table comparing the electrolytes of the blood in the presence of Addison's disease and in the presence of Cushing's syndrome.

Crooke and Callow²²⁴ discussed the diagnosis of Cushing's syndrome, particularly by means of the estimation of urinary androgens. They

223 Anderson, E., Haymaker, W., and Joseph, M. Hormone and Electrolyte Studies of Patients with Hyperadrenocortical Syndrome (Cushing's Syndrome), *Endocrinology* **23** 398-402 (Oct.) 1938. Anderson, E., and Haymaker, W. Adrenal Cortical Hormone (Cortin) in Blood and Urine of Patients with Cushing's Disease, *Proc Soc Exper Biol & Med* **38** 610-613 (June) 1938. Haymaker, W., and Anderson, E. The Syndrome Arising from Hyperfunction of the Adrenal Cortex. The Adrenogenital and Cushing's Syndromes—a Review, *Internat Clin* **4** 244-299 (Dec.) 1938.

224 Crooke, A. C., and Callow, R. K. The Differential Diagnosis of Forms of Basophilism (Cushing Syndrome), Particularly by the Estimation of Urinary Androgens, *Quart J Med* **8** 233-249 (July) 1939.

commented on the clinical difficulty involved in attempting to determine whether the condition is referable to tumor of the adrenal cortex or to a tumor of the basophilic cells of the pituitary body. They proceeded on the hypothesis that the level of urinary excretion of androgens or of closely allied compounds is an index of the activity of the adrenal cortex rather than of gonadal activity. In 1 case, in which an adrenal tumor was present, the urinary excretion of androgens was two or three times the normal amount, after removal of the tumor the value became sub-normal, and within six months it had returned to a normal figure. In the second case, in which an adrenal tumor was present, the androgenic excretion was twenty times normal and later became thirty-five times normal. In the third case, in which an adrenal tumor was not found, the excretion was essentially within normal limits. In the fourth case, in which the patient was suffering from a basophilic adenoma, the androgenic excretion was below normal.

Cantarow²²⁵ studied the concentration of chlorides in the urine of patients who had Cushing's syndrome. He employed the Cutler-Powers-Wilder test and found patients with Cushing's syndrome to be unable to eliminate chloride in the urine in as high a concentration as subjects with no apparent endocrine dysfunction. Cantarow called attention to the possible effect which the sex hormones may play in the urinary excretion of sodium, chloride and potassium, an effect which may be similar to that exerted by the adrenal cortical hormone.

Canelo and Lisser²²⁶ reported a case of arrhenoblastoma in which Cushing's syndrome was simulated. The diagnosis was confirmed at necropsy, and no hyaline changes were found in the basophilic cells of the pituitary body. Elliott and Shallard²²⁷ reported a case of tumor of the adrenal cortex in which Cushing's syndrome was simulated. Reuss, Sigmar and Roller²²⁸ reported an instance in which Cushing's disease was treated with massive doses of estrogen. They concluded that this treatment resulted in the retention of calcium and phosphorus. The study was far from conclusive. Dunn²²⁹ has reported improvement in the treatment of 11 women who had "a benign form of Cushing's syndrome" with the use of large doses of estrogen.

225 Cantarow, A. Urine Chloride Concentration in Patients with Cushing's Syndrome, *Science* **90** 375-376 (Oct 20) 1939

226 Canelo, C K, and Lisser, H. A Case of Arrhenoblastoma Which Simulated Cushing's Disease, *Endocrinology* **24** 838-847 (June) 1939

227 Elliott, G F, and Shallard, B T. Cushing's Syndrome, *M J Australia* **1** 390-393 (Feb 26) 1938

228 Reuss, L, Sigmar, M, and Roller, D. Mineralsalzbilanz bei einem Fall von M. Cushing und Versuch einer Behandlung mit hohen Follikulindosen, *Wien klin Wchnschr* **52** 554-561 (June 9) 1939

229 Dunn, C W. The Cushing Syndrome, *Endocrinology* **22** 374-385 (March) 1938

Kehrer²³⁰ has written a long article on the general subject of Cushing's syndrome, which is recorded here for the benefit of those who may be interested in Kehrer's purely hypothetical concept of the basis of the syndrome. He has attempted to localize the disturbed function to the midbrain but has presented no facts to support his hypothesis.

Summary—The final word on the specific pathologic alterations which occur in the presence of Cushing's syndrome has not yet been spoken. Recent observations suggest that some of the effects of Cushing's syndrome may be mediated through the adrenal cortex. Certainly Kepler has proved that tumors of the adrenal cortex can cause a condition which duplicates the clinical picture of Cushing's syndrome. Additional study of urinary androgens of patients who have Cushing's syndrome, as well as additional observations on the exchange of electrolytes in such patients, ultimately may reveal the specific pathologic lesion (or lesions) in this disease.

POSTERIOR LOBE OF THE PITUITARY BODY AND DIABETES INSIPIDUS

Ranson, Fisher and Ingram²³¹ have reviewed the hypothalamic and hypophyseal mechanism in diabetes insipidus. It is an accepted fact that diabetes insipidus is a result of a deficiency or an absence of the antidiuretic principles of the posterior lobe of the pituitary body. Lesions that interrupt the supraopticohypophyseal tracts produce this disorder. Permanent diabetes insipidus results only if sufficient tissue of the anterior lobe of the hypophysis is left to maintain in animals or in man a fairly normal metabolic activity.

This last fact has been given particular emphasis by Richter²³². Both Richter and Ranson agreed that the polyuria is primary to polydipsia. The maximal diuresis in diabetes insipidus is limited only by the maximal capacity of the kidneys.

Gersh²³³ has studied the relation of the histologic structure to active substances extracted from the posterior lobe of the hypophysis.

230 Kehrer, E. Das Syndrom von Cushing, seine Analyse und Synthese, *Ergebn d inn Med u Kinderh* **55** 178-211, 1938.

231 Ranson, S W, Fisher, C, and Ingram, W R. The Hypothalamicohypophyseal Mechanism in Diabetes Insipidus, *A Research Nerv & Ment Dis, Proc* (1936) **17** 410-432, 1938.

232 Richter, C P. The Pituitary Gland in Relation to Water Exchange. *A Research Nerv & Ment Dis, Proc* (1936) **17** 392-409, 1938.

233 Gersh, I. Relation of Histological Structure to the Active Substances Extracted from the Posterior Lobe of the Hypophysis. *A Research Nerv & Ment Dis, Proc* (1936) **17** 433-436, 1938.

Magoun and associates ²³⁴ have reported their results in the induction of diabetes insipidus in monkeys. They found that the animals could maintain a normal output of urine with the preservation of only a sixth to an eighth of the neurohypophysis, an observation comparable to the demonstrations of physiologic reserve reported for the other organs of the body, including the endocrine glands, by various workers. Magoun and co-workers concluded that the negative results encountered by other investigators in attempting to produce diabetes insipidus by low sections of the stalk are to be explained by the sizable amount of neurohypophysis left proximal to the section connected with the hypothalamus and innervated by the supraoptic nuclei.

Heinbecker and White ²³⁵ studied the effect of deprivation of water on dogs and found that the ability of these animals to concentrate urine was markedly reduced. The importance of this test in the diagnosis of diabetes insipidus in patients has been recently emphasized. Rutledge and Ryneason ²³⁶ and Keller ²³⁷ expressed disagreement with those who hold that the presence of the anterior lobe of the pituitary body is necessary to the production of permanent diabetes insipidus and reported diabetes insipidus in mature dogs studied for six months or longer after complete hypophysectomy.

Ranson and associates ²³⁸ were able to produce both adiposity and diabetes mellitus in the monkey within three weeks after lesions had been caused in the hypothalamus.

Hetherington ²³⁹ produced obesity in only 3 of 51 rats after the injection of chromic acid into the hypophysis. Histologic examination revealed that extensive damage had been done the hypothalamus and hypophyses of the fat rats, whereas among the rats in which obesity was not produced hypothalamic injury was minor or absent, although hypophysial destruction was often severe. No instances of obesity among rats with intact hypophyses were discovered.

234 Magoun, H. W., and Ranson, S. W. The Role of the Supraopticohypophysial Tract and the Neurohypophysis in the Regulation of Water Exchange in the Monkey, *Tr. Am. Neurol. A.* **65** 63-66, 1939. Magoun, H. W., Fisher, C., and Ranson, S. W. The Neurohypophysis and Water Exchange in the Monkey, *Endocrinology* **25** 161-174 (Aug.) 1939.

235 Heinbecker, P. and White, H. L. The Role of the Pituitary Gland in Water Balance, *Ann. Surg.* **110** 1037-1049 (Dec.) 1939.

236 Rutledge, D. I., and Ryneason, E. H. Diabetes Insipidus. II. Treatment by Insufflations of Powdered Posterior Pituitary Substance, *Proc. Staff Meet., Mayo Clin.* **14** 443-446 (July 12) 1939.

237 Keller, A. D. Permanent Diabetes Insipidus Possible in the Absence of the Pars Anterior, *Proc. Soc. Exper. Biol. & Med.* **39** 555-557 (Dec.) 1938.

238 Ranson, S. W., Fisher, C., and Ingram, W. R. Adiposity and Diabetes Mellitus in a Monkey with Hypothalamic Lesions, *Endocrinology* **23** 175-181 (Aug.) 1938.

239 Hetherington, A. W. Obesity in the Rat Following the Injection of Chromic Acid into the Hypophysis, *Endocrinology* **26** 264-268 (Feb.) 1940.

Swann ²⁴⁰ has studied the salt and water metabolism in induced diabetes insipidus in rats. On some rats he performed total nephrectomy, which prevented the polydipsia of both the transient and the permanent phase of the diabetes insipidus, provided the animals were drinking water. If they were drinking saline solution and had come to the permanent phase of diabetes insipidus, nephrectomy did not abolish polydipsia. Swann and Penner ²⁴¹ reported marked aggravation in the symptoms of experimental diabetes insipidus by the administration of sodium chloride.

Swann and Johnson ²⁴² studied the participation of the thyroid gland in diabetes insipidus and corroborated former observations regarding its importance in the exchange of fluids.

Neufeld and Collip ²⁴³ reported the existence of a substance in the posterior lobe of the pituitary body which is antagonistic to hyperglycemia caused by epinephrine. They concluded that it was not similar to the hormone that stimulates metabolism and that it was distinct from vasopressin and oxytocin.

Liu ²⁴⁴ studied pathologic lesions produced in the kidneys by the administration of the pressor principle of the posterior lobe of the pituitary body.

Necheles and Masur ²⁴⁵ produced a hemorrhagic condition of the entire gastrointestinal tract of dogs by the administration of acetylcholine and pitressin.

Elsom, Glenn and Drossner ²⁴⁶ commented on the stimulating effect which pitressin and amphetamine sulfate exert on the motor activity of the small intestine and the colon.

240 Swann, H. G. Some Experiments on Salt and Water Metabolism in Diabetes Insipidus, *Endocrinology* **25** 288-295 (Aug.) 1939.

241 Swann, H. G., and Penner, B. J. The Effect of Salts on the Diabetes Insipidus Following Posthypophysectomy in the Rat, *Endocrinology* **24** 253-259 (Feb.) 1939.

242 Swann, H. G., and Johnson, P. E. Thyroid Function in Diabetes Insipidus in the Rat, *Endocrinology* **24** 397-403 (March) 1939.

243 Neufeld, A. H., and Collip, J. B. The Antagonist to Adrenalin Hyperglycaemia in Pituitary Extracts, *Canad. M. A. J.* **40** 537-539 (June) 1939, Further Studies on the Antagonist to Adrenalin Hyperglycemia in Pituitary Extracts, *Endocrinology* **25** 775-781 (Nov.) 1939.

244 Liu, S. H. Pathological States Produced by Administration of Posterior Pituitary Pressor Principle, *Chinese M. J.* **55** 448-464 (May) 1939.

245 Necheles, H., and Masur, W. Gastro-Intestinal Pathology in Dogs Following Administration of Acetylcholine and Pitressin, *Am. J. Digest. Dis.* **6** 389-391 (Aug.) 1939.

246 Elsom, K. A., Glenn, P. M., and Drossner, J. L. Intubation Studies of Human Small Intestine. XVIII. The Effect of Pitressin and of Amphetamine (Benzedrine) Sulphate on the Motor Activity of the Small Intestine and Colon, *Am. J. Digest. Dis.* **6** 593-597 (Nov.) 1939.

Shapiro²⁴⁷ found that estradiol benzoate in large doses caused a significant decrease in the severity of diabetes insipidus. Because of the known antagonism between the estrogenic hormones and principles of the anterior lobe of the pituitary body, he received this reduction as evidence that there is a diuretic action of the anterior lobe.

Winter, Ingram and Gross²⁴⁸ studied the effect of injections of pitressin on serum electrolytes and the exchange of water in cats with diabetes insipidus and adrenal insufficiency. They found that by the use of pitressin they could increase the survival time of adrenalectomized cats with experimentally induced diabetes insipidus, and they expressed the opinion that the increase in survival time was an expression of improvement in the ability of the animals to retain sodium and chloride.

Silvette and Britton²⁴⁹ advanced the hypothesis that in the excretion of water and sodium by the kidney, the diuretic hormone of the adrenal cortex acts in physiologic antagonism to the antidiuretic hormone of the posterior lobe of the pituitary body. They said they considered the normal secretion of both of these hormones necessary to the proper maintenance of sodium chloride and water balance in the body.

In a later paper Corey, Silvette and Britton²⁵⁰ presented additional observations to support this concept.

Wermer²⁵¹ postulated the existence of two types of diabetes insipidus—one caused by the absence of the antidiuretic hormone of the posterior lobe of the hypophysis and the other by an excessive amount of the diuretic hormone of the anterior lobe of the pituitary body.

Boyd and Whyte,²⁵² using frogs as the experimental animal, achieved results which caused them to believe that there are two principles involved in water balance, one causing retention of water and the other stimulating secretion of sodium chloride.

247 Shapiro, B. G. Control of Urinary Secretion by the Anterior Pituitary, *Lancet* **2** 1457-1460 (Dec. 24) 1938.

248 Winter, C. A., Ingram, W. R., and Gross, E. G. Effect of Pitressin Injections upon Serum Electrolytes and Water Exchange of Cats with Diabetes Insipidus and Adrenal Insufficiency, *Am J Physiol* **127** 64-70 (Aug.) 1939.

249 Silvette, H., and Britton, S. W. Renal Function in the Opossum and the Mechanism of Cortico-Adrenal and Post-Pituitary Action, *Am J Physiol* **123** 630-639 (Sept.) 1938.

250 Corey, E. L., Silvette, H., and Britton, S. W. Hypophyseal and Adrenal Influence on Renal Function in the Rat, *Am J Physiol* **125** 644-651 (April) 1939.

251 Wermer, P. Hypophyse und Wasserhaushalt, *Wien Arch f inn Med* **32** 189-214, 1938.

252 Boyd, E. M., and Whyte, D. W. The Effect of Posterior Hypophyseal Extract on the Retention of Water and Salt Injected into Frogs, *Am J Physiol* **125** 415-422 (March) 1939.

Pickford²⁵³ reported the inhibitory effect of acetylcholine on water diuresis in dogs and found that this effect could not be obtained in the absence of the posterior lobe of the pituitary gland

Necheles and Neuwelt²⁵⁴ attacked this problem in a different way, for they were able by the injection of pitressin (but not pitocin) to prevent the effect of acetylcholine

Kuschinsky and Bundschuh²⁵⁵ wrote that in the posterior lobe of the hypophysis there is a substance having a diuretic effect which in their opinion is entirely separate from the antidiuretic effect of pitressin and also differs from the effect of oxytocin. The oxytocic hormone has received additional study by Haterius and Ferguson²⁵⁶ and by Stehle and Trister²⁵⁷

Bundschuh and Kuschinsky²⁵⁸ reported that after increased injection of sodium chloride the urine of rats contained active substances which resembled the vasopressor and the oxytocic principle. In the urine of normal human beings and rats only an oxytocic-like substance can be demonstrated

Ingram and associates²⁵⁹ found that normal cats subjected to conditions producing dehydration excrete appreciable quantities of an antidiuretic substance in the urine. Cats having diabetes insipidus referable to interruption of the supraopticohypophysial tract without direct injury to the pituitary body do not excrete this antidiuretic substance after dehydration. According to the observations of those investigators, when commercial preparations of the posterior lobe of the pituitary body are injected into normal cats and into cats with diabetes insipidus the antidiuretic substance appears in the urine in relatively small quantities. The results were interpreted as offering support for the suggestion of

253 Pickford, M. The Inhibitory Effect of Acetylcholine on Water Diuresis in the Dog and Its Pituitary Transmission, *J Physiol* **95** 226-238 (Feb 14) 1939

254 Necheles H., and Neuwelt F. Antagonism Between Posterior Pituitary Secretion and Acetylcholine. *Am J Physiol* **124** 142-148 (Oct) 1938

255 Kuschinsky, G., and Bundschuh, H. E. Ueber die diuretische Wirkung von Hinterlappen-Präparaten und ihre Beziehung zur antidiuretischen Wirkung des Vasopressins, *Klin Wchnschr* **18** 207-208 (Feb 11) 1939

256 Haterius H. O. and Ferguson J. K. W. Evidence for Hormonal Nature of Oxytocic Principle of Hypophysis. *Am J Physiol* **124** 314-321 (Nov) 1938

257 Stehle R. L., and Trister S. M. Additional Data Concerning the Chemistry of the Pressor and Oxytocic Hormones of the Pituitary Gland. *J Pharmacol & Exper Therap* **65** 343-352 (April) 1939

258 Bundschuh H. E. and Kuschinsky G. Ueber den Gehalt des Harnes an hinterlappenähnlichen Wirkstoffen. *Klin Wchnschr* **18** 251-252 (Feb 18) 1939

259 Ingram, W. R. Ladd, L. and Benbow J. T. The Excretion of Anti-diuretic Substances and Its Relation to the Hypothalamico-Hypophyseal System in Cats, *Am J Physiol* **127** 544-551 (Oct) 1939

Goodman and Gilman, made in 1937, that the neurohypophysis may respond to the need for conservation of water by secreting increased amounts of diuretic substance, and as indicating that the supraoptico-hypophysial tract is necessary for this response

Teel and Reid ²⁶⁰ studied the urine of patients suffering from pre-eclampsia and eclampsia and found a marked antidiuretic effect of concentrates of such urine

Warkany and Mitchell ²⁶¹ have reviewed the literature relating particularly to the clinical manifestations of diabetes insipidus. They emphasized the value of the urinary concentration test as a means of distinguishing true diabetes insipidus from nervous polyuria

MacPheison ²⁶² reported another instance of a patient who had both diabetes mellitus and diabetes insipidus. Postmortem examination showed slight enlargement of the anterior lobe of the hypophysis, with hyperplasia of eosinophilic cells

Greene and Gibson ²⁶³ have recorded all the known cases of the coexistence of these two diseases. Rutledge and Rynearson ²⁶⁴ added a recent case

Papers continue to be published indicating the existence of a possible relation of the posterior lobe of the pituitary body to widely separated conditions. Kramer, Grossman and Parker ²⁶⁵ advocated the intranasal use of solution of posterior pituitary of twice the U. S. P. concentration pituitrin (surgical) and of adrephine (a mixture of 1:10,000 solution of epinephrine hydrochloride and 2 per cent ephedrine sulfate, with 0.5 per cent chlorobutanol as preservative) as a protection against poliomyelitis

260 Teel, H. M., and Reid, D. E. Observations upon the Occurrence of an Antidiuretic Substance in the Urine of Patients with Pre-Eclampsia and Eclampsia, *Endocrinology* **24** 297-310 (March) 1939

261 Warkany, J., and Mitchell, A. G. Diabetes Insipidus in Children. A Critical Review of Etiology, Diagnosis and Treatment, with Report of Four Cases, *Am J Dis Child* **57** 603-666 (March) 1939

262 MacPherson, E. Case of Diabetes Mellitus Associated with Lesions of the Pituitary Body, *Glasgow M J* **131** 220-224 (May) 1939

263 Greene, J. A., and Gibson, R. B. Coexistence of Diabetes Mellitus and Diabetes Insipidus. Report of a Case with Pregnancy, *J Lab & Clin Med* **24** 455-457 (Feb) 1939

264 Rutledge, D. I., and Rynearson, E. H. Diabetes Insipidus. I. Coexistence of Diabetes Mellitus and Diabetes Insipidus, *Proc Staff Meet, Mayo Clin* **14** 441-443 (July 12) 1939

265 Kramer, S. D., Grossman, L. H., and Parker, G. C. Evidence of Active Immunity to Experimental Poliomyelitis Obtained by the Intranasal Route in *Macacus Rhesus*, *J Exper Med* **67** 529-544 (April) 1938

Potter and Mueller ²⁶⁶ reviewed the use of pitressin in abdominal surgical procedures, reporting its routine use in 2,500 abdominal operations

Metz and Lackey ²⁶⁷ treated with insufflations of posterior pituitary 42 patients who had peptic ulcer and reported satisfactory clinical results for 40 of them

Metz ²⁶⁸ later reported the production of gastric lesions by the use of an extract of the posterior lobe of the pituitary body. The study was performed on rabbits, and far larger doses of the extract were given than were used in the treatment of patients. Portnoy ²⁶⁹ reported success in the treatment of herpes zoster with solution of posterior pituitary, either of U S P concentration or of double strength. Cook and Stoesser ²⁷⁰ reported improvement in bronchial asthma with the use of this extract

The method of administering preparations of the posterior lobe of the pituitary body is becoming variable. Many physicians employ hypodermic injection as the method of choice. Administration by intranasal insufflation of posterior pituitary powder is generally regarded as the best method, because it is effective, easy to use and inexpensive.

Court and Taylor ²⁷¹ have prepared an emulsion with wool fat and beeswax as its base, which is injected subcutaneously, and they reported a desirable delayed absorption as produced by it. Wankmuller ²⁷² outlined a method of intramuscular injection, also utilizing an emulsion. Von Matolay ²⁷³ transplanted half the pituitary body of a cat to the posterior part of the sheath of the rectus muscle and claimed a startling improvement.

266 Potter, P. C., and Mueller, R. S. The Value of Pitressin in Abdominal Surgery, with Special Reference to Dosage and Technique, *Am J Surg* **43** 710-713 (March) 1939

267 Metz, M. H., and Lackey, R. W. Peptic Ulcer Treated by Posterior Pituitary Extract, Two Years' Experience, *Texas State J Med* **34** 214-220 (July) 1938

268 Metz, M. H. Gastric Lesion Produced by Posterior Pituitary Extract, *Texas State J Med* **34** 295-297 (Aug) 1938

269 Portnoy, S. H. Some Experiences with Posterior Pituitary Solution in Herpes Zoster, *J Med* **18** 619-620 (Feb) 1938

270 Cook, M. M., and Stoesser, A. V. Influence of Induced Variations in Electrolyte and Water Exchanges with Pitressin in Bronchial Asthma, *Proc Soc Exper Biol & Med* **38** 636-638 (June) 1938

271 Court, D., and Taylor, S. A. Diabetes Insipidus Treated by Slowly Acting Pituitary Emulsion, *Proc Roy Soc Med* **32** 1203-1206 (Aug) 1939

272 Wankmuller, R. Ueber die Wirksamkeit eines Tonephindopots beim Diabetes Insipidus, *Klin Wchnschr* **18** 566-568 (April 22) 1939

273 von Matolay, G. Transplantationen von Kalbshypophysen bei Diabetes insipidus, *Arch f klin Chir* **191** 73-78, 1938

Jones²⁷⁴ described a new syndrome, which he considered to be, apparently, referable to overactivity of the posterior lobe of the pituitary body. He reported on patients suffering from hypertension, hypochromic anemia, achlorhydria (with histamine) and abnormal carbohydrate metabolism. He obtained from the urine of patients an extract which caused persistent elevation of blood pressure in the cat, the electrocardiographic tracings being essentially similar to those obtained from subjects affected by extract of the posterior lobe of the pituitary body. This extract from the patient's urine also had a pronounced antidiuretic action when it was injected into rats. The pressor action was unaffected by boiling, pitressin is likewise unaffected by boiling. The melanophore-dispersing action of the extract was demonstrated by the darkening obtained in frogs.

Summary—Although the role of the posterior lobe of the pituitary body in the causation of diabetes insipidus is an accepted fact, the role of this lobe in the metabolism of water and sodium chloride is not entirely clear. Since the number of substances assigned to this lobe is increasing, the greatest caution in evaluating such observations is desirable. The exact origin of secretions assigned to the posterior lobe still needs to be clarified.

MISCELLANEOUS

Rasmussen's²⁷⁵ report of the innervation of the hypophysis constitutes another of his classic studies. He found an enormous nerve supply to the posterior (neural) lobe, but noted that only a few nerve fibers pass through the intermediate region so that they reach slightly into the anterior lobe, the number is negligible. Such a large proportion of the anterior lobe appears to be devoid of nerve fibers that the existence of secretory nerves to this part of the hypophysis remains highly questionable.

Sutton and Brief²⁷⁶ studied the cellular and physiologic changes in the anterior lobe of the hypophysis of rats deficient in vitamin A and found a significant increase in the basophilic cells in both sexes, the increase was greater in the male animals. The authors interpreted the results as indicating that deficiency of vitamin A produces a partial "castration effect" on the hypophysis. With vitamin A deficiency the content of gonadotropic hormone of the pituitary body is increased.

274 Jones, E. I. A New Syndrome Apparently Due to Over-Activity of the Posterior Pituitary, *Lancet* **1** 11-13 (Jan 1) 1938.

275 Rasmussen, A. T. Innervation of the Hypophysis, *Endocrinology* **23** 263-278 (Sept) 1938.

276 Sutton, T. S., and Brief, B. J. Cellular Changes in the Anterior Hypophyses of Vitamin A-Deficient Rats, *Endocrinology* **23** 211-215 (Aug) 1938, Physiological Changes in the Anterior Hypophysis of Vitamin A-Deficient Rats, *ibid* **25** 302-307 (Aug) 1939.

This increase in potency is greater in the male than in the female. Sure²⁷⁷ observed the influence of avitaminosis on the weights of the endocrine glands. In vitamin A deficiency he found hypertrophy of the pancreas amounting to 40 per cent. In the presence of vitamin B₁ deficiency there is marked hypertrophy of the thyroid and adrenal glands, with decided atrophy of the thymus gland. Hypertrophy of the pituitary body was found in the presence of vitamin B₁ and vitamin G (B₂) deficiency to the extent of 40 and 25 per cent, respectively. Repeated depletions of vitamin B₁ have the following influence on weights of endocrine glands. The hypertrophy of the pituitary body entirely disappears, the thyroid gland is diminished to insignificant proportions and hypertrophy of the adrenal glands is reduced from 50 to 20 per cent.

Culmer and associates²⁷⁸ reported depression of gastric secretion obtained by the gonadotropic fraction of urine obtained during pregnancy. It is concluded that this fraction contains a substance which suppresses the gastric secretory response of a dog to a test meal. The nature of the substance and its mechanism of action are problematic.

Plattener and Reed²⁷⁹ observed muscular efficiency in rats into which anterior pituitary growth factor had been injected. In spite of their having greater average size, the animals which had received injections had no physiologic advantage over the untreated controls.

Ingle²⁸⁰ studied the work performance of untreated hypophysectomized rats. There was a marked decrease in the capacity for work when total hypophysectomy had been performed. The study indicated that if half of the anterior lobe of the hypophysis is left intact the work performance of the rat is carried out at a nearly normal rate.

Rogers²⁸¹ has outlined another method for studying endocrine effects utilizing observations of changes in the electrical potential during the estrous cycle. He concluded

That hypophysectomy has the same effect on the electrical potential as ovariectomy and that, as in castrate animals, the normal estrous pattern of electrical

277 Sure, B. Influence of Avitaminoses on Weights of Endocrine Glands, *Endocrinology* **23** 575-580 (Nov.) 1938.

278 Culmer, C. U., Atkinson, A. J., and Ivy, A. C. Depression of Gastric Secretion by the Anterior Pituitary-Like Fraction of Pregnancy Urine, *Endocrinology* **24** 631-637 (May) 1939.

279 Plattener, E. B., Reed, C. I., Brown, A. W., and Evans, H. A Study of Muscular Efficiency in Rats Injected with Anterior Pituitary Growth Factor, *Endocrinology* **25** 401-404 (Sept.) 1939.

280 Ingle, D. J. The Work Performance of Untreated Hypophysectomized Rats, *Endocrinology* **22** 465-468 (April) 1938.

281 Rogers, P. V. Changes in Electrical Potential During the Estrous Cycle of the Rat. II. Partial and Complete Hypophysectomy and Pituitary Replacement Therapy, *Endocrinology* **22** 35-40 (Jan.) 1938.

potential may be reproduced by injections of theelin or prephysin, and also that as little as 0.5 per cent of anterior pituitary is sufficient to cause luteinization after the ovarian follicles have been matured with prephysin

Cutting and Lewis²⁸² reported the failure of the anterior lobe of the pituitary body to produce hormones by the tissue culture technic

Bischoff and Long²⁸³ studied the endocrine factors influencing the development of tumors and concluded

That the endogenous production of estrin and its related compounds by the ovary through prolactin stimulation does not influence carcinogenesis, and that the production of carcinogenesis by massive doses of estrin (exogenous) may be without physiologic significance

Twort and Lasnitzki²⁸⁴ studied the weight of the pituitary body in rats inoculated with a transmissible tumor. They found that on the average the ratio of pituitary dry weight to brain weight was usually smaller in groups of animals having tumors than in those not having tumors. In most instances the relative weight of the pituitary body in the female animal was found to be greater than that in the male animal. Sittenfield²⁸⁵ and Cramer and Horning²⁸⁶ also have studied the relation between hormones and the growth of tumors

Observations continue to be reported indicating the relation of seasons, hibernation, light and other factors to the endocrine glands. Foster and associates²⁸⁷ attempted to induce hibernation but found that this could not be accomplished during the breeding season. There was a maximal tendency to hibernate, which persisted until the onset of genital enlargement. The studies of those investigators suggested that inactivity of the pituitary body is the primary factor responsible for the

282 Cutting, W. C., and Lewis, M. R. Failure of the Anterior Lobe of Pituitary to Produce Hormones in Tissue Culture, *Arch f exper Zellforsch* **21** 523-524, 1938

283 Bischoff, F., and Long, M. L. Endocrine Factors Influencing Tumor Development. The Effect of Prolactin upon the Marsh-Buffalo Adenocarcinoma, *Endocrinology* **23** 327-329 (Sept) 1938

284 Twort, J. M., and Lasnitzki, M. Studies on the Pituitary Weight of Rats Inoculated with a Transmissible Tumor, *Endocrinology* **23** 87-90 (July) 1938

285 Sittenfield, M. J. The Influence of the Anterior Lobe of the Pituitary on the Growth of Sarcoma and Carcinoma, *A Research Nerv & Ment Dis, Proc* (1936) **17** 466-470, 1938

286 Cramer, W., and Horning, E. S. The Prevention of Spontaneous Mammary Cancer in Mice by the Thyrotropic Hormone of the Pituitary Gland, *Lancet* **1** 72-76 (Jan 8) 1938

287 Foster, M. A., Foster, R. C., and Meyer, R. K. Hibernation and the Endocrines, *Endocrinology* **24** 603-612 (May) 1939

phenomenon of hibernation Bissonnette,²⁸⁸ Riley and Witschi²⁸⁹ and Benoit and Kehl²⁹⁰ have observed the effect of light on the hypophysis and its hormones Raab²⁹¹ has attempted to study the relation between light stimuli and metabolism of man The eyes of the patients to be studied were taped for a period varying between seven and fifteen days During this "black out," a marked decrease in blood sugar occurred Other changes took place in the values for sugar tolerance and blood cholesterol and in the blood pressure and basal metabolic rate

Képinov,²⁹² in studying the effect of insulin on epinephrine and in observing glycogenolysis in the liver of the frog as influenced by the administration of extracts of the anterior lobe of the pituitary body, has found that there is a marked difference from one season to another His studies indicated that in frogs in the summer glycogenolysis occurs after a perfusion of the liver with insulin and Locke-Tyrode solution for twenty-five to thirty minutes, whereas in frogs in the winter four to five hours is required for this effect Extracts of the anterior lobe of the pituitary body suppressed the antiglycogenolytic effects of insulin

D'Amour and D'Amour²⁹³ have assayed the potency of certain commercial hormone preparations They concluded their paper as follows

The authors believe that the manufacturers of commercial hormone preparations are making an honest and sincere effort to produce dependable therapeutic agents No one who is acquainted with the men connected with these organizations or who is familiar with the large amount of research which they have devoted to this problem could believe otherwise At the same time, they themselves would no doubt be the last to assert that complete success had been achieved

In the light of the present study, we believe that two general criticisms are justified Extracts of the anterior lobe, both gonadotropic and growth, and aqueous estrin preparations, appear to deteriorate on standing This problem deserves study and if the time during which activity is retained can be determined it would be well to place an expiration date on the containers

288 Bissonnette, T H Influence of Light on the Hypophysis Effects of Long-Contained "Night-Lighting" on Hypophysectomized Female Ferrets and Those with Optic Nerves Cut, *Endocrinology* **22** 92-103 (Jan) 1938

289 Riley, G M, and Witschi, E Comparative Effects of Light Stimulation and Administration of Gonadotropic Hormones on Female Sparrows, *Endocrinology* **23** 618-624 (Nov) 1938

290 Benoit, J, and Kehl, R Nouvelles recherches sur les voies nerveuses photoreceptrices et hypophysostimulantes chez le canard domestique, *Compt rend Soc de biol* **131** 89-93, 1939

291 Raab, W Zur Frage Licht und Stoffwechsel des Menschen, *Ztschr f d ges exper Med* **106** 154-166, 1939

292 Kepinov, L Nouvelles recherches sur l'action antiglycogenolytique de l'insuline Suppression de l'effet antiglycogenolytique de l'insuline par l'extrait antehypophysaire, *Compt rend Soc de biol* **128** 331-334, 1938

293 D'Amour, F E, and D'Amour, M C The Potency of Certain Commercial Hormone Preparations, *Endocrinology* **22** 583-587 (May) 1938

In the second place, the criticism of lack of uniformity in assay methods and units should be met. In the case of estrin, the Health Organization of the League of Nations has adopted a unit and, in time, official action regarding other hormones will probably be taken. In the meantime, however, to the non-commercial individual, at least, there appears to be no valid reason why the leading firms should not agree upon uniform methods of assay and upon standard units. Other industries have adopted rules of standard practice to which all members conform, with benefit to themselves and to the consumer.

Gaensbauer and Bradbury²⁹⁴ have also assayed the comparative potency of products of the anterior lobe of the pituitary body. Bergman and associates²⁹⁵ have discussed the efficiency of extraction and separation of certain hormones of the anterior lobe of the pituitary body. Saxton and Greene²⁹⁶ observed the age and sex differences in the content of hormone in the hypophysis of the rabbit. Halpern²⁹⁷ discussed quantitative cytologic studies on the anterior lobe of the hypophysis of fetuses and of children, correlated with sexual and skeletal development.

Sorsby, Avery and Cockayne²⁹⁸ have reviewed the literature on the Laurence-Moon-Biedl syndrome. Boswell²⁹⁹ reported the results of roentgen therapy administered to the pituitary and adrenal regions in the treatment of essential hypertension. In common with those of other reports of this type, the results are unconvincing. Waldorp and associates³⁰⁰ reported the results of treatment of patients who displayed a variety of endocrine syndromes by the implantation of bovine pituitary bodies. He and his colleagues treated patients suffering from many conditions, from Simmonds' disease to alopecia, and, of course, reported improvement in most instances.¹

294 Gaensbauer, F, and Bradbury, J T. Comparative Potency of Commercial Anterior Pituitary-Like Preparations, *Endocrinology* **24** 867-871 (June) 1939.

295 Bergman, A J, Houchin, O B, and Turner, C W. Efficiency of Extraction and Separation of Certain AP Hormones, *Endocrinology* **25** 547-553 (Oct) 1939.

296 Saxton, J A, Jr, and Greene, H S N. Age and Sex Difference in Hormone Content of the Rabbit Hypophysis, *Endocrinology* **24** 494-502 (April) 1939.

297 Halpern, S R. Quantitative Cytological Studies of the Anterior Lobe of the Hypophysis of Fetuses and Children, Correlated with Sexual and Skeletal Development, *Endocrinology* **22** 173-180 (Feb) 1938.

298 Sorsby, A, Avery, H, and Cockayne, E A. Obesity, Hypogenitalism, Mental Retardation, Polydactylia and Retinal Pigmentation (Laurence-Moon-Biedl Syndrome), *Quart J Med* **8** 51-68 (Jan) 1939.

299 Boswell, F P. Results of Roentgen Therapy in Essential Hypertension, *Indust Med* **7** 251-253 (May) 1938.

300 Waldorp, C P, Reforzo Membrives, J, and Luchetti, S E. Resultados personales de la implantación de hipofisis bovina en el ser humano, *Prensa med argent* **26** 1179-1194 (June 21) 1939.

Maranon, Richet, Sourdel and Netter ³⁰¹ discussed pigmentary disturbances of pituitary origin in human beings and presented the histories of 2 patients. One was a man who was struck on the right parietal region. He was unconscious for five or six hours. Diabetes insipidus developed, which responded to injections of solution of posterior pituitary. Later epileptic seizures occurred, and at this time a strange pigmentation appeared, it resembled vitiligo and appeared about twenty days after the accident. Five days later cranial decompression was performed, and within two weeks there was a slow but unmistakable decrease in the pigmentary disturbance. About two months after the accident the patient was able to return to work. The epileptic seizures had not returned at the time Maranon and his associates wrote, and the pigmentation had entirely disappeared. The second patient also had suffered fracture of the skull, with subsequent development of diabetes insipidus. Pigmentary disturbance likewise developed, which was described as a "melanoderma," it was entirely different from that seen in the presence of any known disease and is described in detail in the article. These lesions did not disappear, but varied without any apparent relation to the changes in the other symptoms.

Teague ³⁰² has studied the relation of the melanophore hormone of the pituitary body to the oxygen consumption of the rat. Hanes and Crew ³⁰³ discussed endocrinologic and metabolic observations made in cases of exfoliative dermatitis. Vollmer, Gordon, Levenstein and Charipper ³⁰⁴ studied the effects of hypophysectomy on the blood picture of the rat. Flaks, Himmel and Zotnik ³⁰⁵ recorded their evidence in favor of a hemopoietic hormone of the anterior lobe of the pituitary body.

Dohan, Jeffers and Creskoff ³⁰⁶ found that no increase in blood pressure, in erythrocytes, reticulocytes or hemoglobin was produced by the

301 Maranon, G., Richet, C., Sourdel, M., and Netter, H. Les troubles pigmentaires d'origine hypophysaire en clinique humaine, *Presse méd* **45** 1883-1885 (Dec 29) 1937.

302 Teague, R. S. The Relation of the Melanophore Hormone of the Pituitary Gland to Oxygen Consumption of the Rat, *Endocrinology* **25** 953-961 (Dec) 1939.

303 Hanes, W. J., and Crew, R. S. Endocrinologic and Metabolic Observations in Exfoliative Dermatitis, *Endocrinology* **24** 404-413 (March) 1939.

304 Vollmer, E. P., Gordon, A. S., Levenstein, I., and Charipper, H. A. Effects of Hypophysectomy upon the Blood Picture of the Rat, *Endocrinology* **25** 970-977 (Dec) 1939.

305 Flaks, J., Himmel, I., and Zotnik, A. La polyglobulie provoquée par les extraits de lobe antérieur d'hypophyse prouve l'existence d'une hormone hémo-poétique, *Presse med* **46** 1506-1509 (Oct 12) 1938.

306 Dohan, F. C., Jeffers, W. A., and Creskoff, A. J. Blood Pressure and Hematology in Dogs Injected with Anterior Pituitary Extract, *Proc Soc Exper Biol & Med* **39** 327-329 (Nov) 1938.

repeated injection of an active saline extract of the anterior lobe of the pituitary body. Their reports did not confirm the assumption that excessive amounts of extract of the anterior lobe of the pituitary body may induce polycythemia. Sharp and Mack³⁰⁷ discussed the relation of hemopoietic phenomena to endocrine disorders in women. The presentation is largely hypothetic. Snapper, Groen, Hunter and Witts³⁰⁸ reported on 6 patients who had pituitary and gonadal insufficiency as well as associated achlorhydria, anemia and subacute combined degeneration of the spinal cord. Lawrence and Van Wagenen³⁰⁹ reported on 5 patients who had tumors of the pituitary body and associated anemia. Wetzler-Ligetı and Wiesner³¹⁰ reported on the increased activity of the reticuloendothelial system following the injection of certain extracts of the anterior lobe of the pituitary body.

CONCLUSION

It must be apparent that in the years 1938 and 1939 no startling developments occurred which are likely to be of any value in treating patients during 1940. The aforementioned years have been valuable, however, in that efforts of workers in the "fundamental fields" continued to increase knowledge of the function of the anterior lobe of the pituitary body. Young's production of permanent diabetes mellitus is outstanding. It has been equally encouraging to note the growth of conservatism (and skepticism) in the minds of practicing physicians. Papers continue to appear recording the indiscriminate administration of unknown substances for the treatment of unknown conditions, but such publications are receiving less attention. The best papers are now recognized as being those which adhere to known fundamental principles and which manifest an interest in facts rather than in assumptions. Much that is written about the hypophysis is hypothesis.

307 Sharp, E. A., and Mack, H. C. The Relationship of Hemopoietic Phenomena to Endocrine Disorders in Women, *Endocrinology* **24** 202-218 (Feb) 1939.

308 Snapper, I., Groen, J., Hunter, D., and Witts, L. J. Achlorhydria, Anaemia and Subacute Combined Degeneration in Pituitary and Gonadal Insufficiency, *Quart J Med* **6** 195-209 (April) 1937.

309 Lawrence, J. S., and Van Wagenen, W. P. Hematopoietic Changes Associated with Pituitary Disease, *Tr A Am Physicians* **53** 152-156, 1938.

310 Wetzler-Ligetı, C., and Wiesner, B. P. Restropic Effects of Anterior Lobe Extracts, *Endocrinology* **22** 693-702 (June) 1938.

Book Reviews

Practical Bacteriology, Haematology and Animal Parasitology By E R Stitt, M D , Paul W Clough, M D , and Mildred C Clough, M D Ninth edition Price \$7 00 Pp 961, with 208 illustrations Philadelphia P Blakiston's Sons & Co , 1938

Thirty years ago, Stitt published the first edition of "Bacteriology, Blood Work and Animal Parasitology," containing 245 pages and four plates. This edition received such universal support that the next year the second edition appeared, with 365 pages and 91 illustrations. Since that time there have been seven other editions, including the present. As these various editions give an accurate insight into the knowledge of the discussed subjects at the time, one may follow the progress of bacteriology, hematology and parasitology in the last three decades merely by reviewing the various editions in order.

The ninth edition is divided into four parts plus an appendix. Part 1 deals with bacteriology, considering first a classification of bacteria, with comments on the various methods of classification. Following this classification, the various bacteria are discussed with reference to the diseases they cause. Each discussion includes a description of the character of the lesion produced, the laboratory means of isolating and identifying the causative agents and serologic tests and other laboratory procedures used to identify the disease, and concluding each discussion is a short résumé of the treatment. One chapter deals with serologic methods, first defining the various terms used and then discussing various technics, with interpretation of the findings. In this chapter is found a discussion of anaphylaxis, hay fever and the complement fixation test. Of significance to both clinicians and clinical pathologists are the authors' suggestion for the conservative interpretation of the Wassermann reaction and the evaluation of the complement fixation and the various flocculation tests for syphilis.

Part 2 describes the various technics employed in hematology, then there follows a discussion of the interpretation of the hemogram with the prognostic indications of the leukocyte count. The anemias are classified according to cause, and each is described with special reference to the blood findings.

Part 3, after presenting a treatise on the classification of animal parasites, with a discussion of the nomenclature, offers a table which is useful to the investigator, as it outlines definite host, intermediate host, the reservoir of the virus and the transmission and pathogenicity of the protozoa, cestodes and nematodes. Also included is a discussion of the arthropodan diseases, with the life history and disease manifestations of each. Following this is a fuller description of the various protozoa and diseases produced. This part of the work is most elaborate and comprehensive.

In part 4 are considered the clinical and the pathologic examinations of the various fluids and organs of the body, including the examination of exudates from infectious processes found on and within the body for the purpose of determining the etiologic factors, and the routine examination of spinal fluid. The remainder of this section of the book deals with procedures common to clinicolaboratory medicine, including blood chemistry, urinalysis, renal function tests, gastric content analysis, examination of feces and basal metabolism and its relation to various endocrine disorders. The avitaminoses are considered. Each disease is discussed from the standpoint of the clinical picture presented, the pathologic changes, etiology and the laboratory procedures necessary to identify the disease, finally, there is a small paragraph on treatment of the various diseases discussed.

The appendix deals entirely with laboratory technic, confined to the care of instruments, sterilization and preparation of mediums and staining reagents.

This edition is characterized by the brief, concise and comprehensive way in which it is compiled. It should enjoy prestige to an even greater extent than the previous editions. It is heartily recommended as a text for students and as a reference text for both clinicians and laboratory workers.

Die Grundlagen der neuzeitlichen Ernährung des Deutschen Menschen
Ein Leitfaden für Studierende und Ärzte By Dr. Ferdinand Bertram
 Price, 5.80 marks, boards Pp 140 Leipzig Georg Thieme, 1939

The author of this manual, a recognized authority on diabetes, is physician in chief to the Second Medical Division of the Barnbeck General Hospital, Hamburg, and also professor of internal medicine.

The book includes a general review of the pathogenesis of hyperglycemia, glycosuria and acidosis, a discussion of the etiology, pathology and complications of diabetes and a detailed description of the author's therapeutic procedure. A very brief section is allotted to diabetes in children and another to prognosis. More attention to documentation would be appreciated. The bibliography is limited to a few monographs and less than a dozen general articles, mostly German.

The therapeutic procedure is sound for the most part. Exception may be taken to the objection of the author to having patients test their own urine. It is the opinion of leading American authorities on diabetes that the patient must keep himself continually informed on the state of his urine, in order to be able to regulate successfully the doses of insulin. Bertram states the belief that the sense of well-being of the patient provides a sufficient measure of safety for the adjustments of food and insulin and suggests that testing the urine may provoke "anticipation glycosuria." He makes a good point in demanding that the objective of treatment in diabetes must be to equip the patient for a practical life and not for the life of an invalid, and he believes that protamine zinc insulin is useful in attaining this objective.

In mild cases Bertram gives a single dose of "depot insulin" from the beginning of treatment. In cases of moderate and greater severity he first secures control by using four doses of unmodified insulin, giving one of these at 2 o'clock in the morning, then he substitutes "depot insulin" in two doses and finally attempts to give all the insulin required for the day in one dose. However, in a number of severe cases control with one dose of protamine zinc insulin a day has not been possible.

Among the complications attending treatment with insulin is a form of lipodystrophy, for which heretofore no satisfactory treatment has been found. Agreeing with other authors, Bertram believes that the disturbance is of nervous origin. Further evidence of this is supplied by one of his cases in which such atrophy of fat was successfully combated by giving large doses of thiamine chloride. Bertram also uses large doses of thiamine chloride in treating diabetic neuritis. He describes the results as being promptly favorable. (The reviewer has not had much success with this procedure and considers inconclusive the evidence that diabetic neuritis is often related to vitamin deficiency.)

The book contains much other comment of interest and deserves careful reading.

Architecture of the Kidney in Chronic Bright's Disease By Jean Oliver
 Price, \$10 Pp 256, with 112 illustrations New York Paul B Hoeber, Inc., 1939

Oliver has brought together his studies on the structure of the chronically diseased kidney. Many have been published previously in articles appearing since 1930 in the medical literature. The author correlates these numerous publications and adds data previously unpublished. The book is divided into eight chapters, the contents of which are suggested by the titles, which follow: Introduction, The Two Architectural Units of Chronic Bright's Disease, The Morphology of the Abnormal Nephron, The Agglomerular Nephrons of Terminal Bright's Dis-

case, The Transformation of the Arterial System in Terminal Bright's Disease, Factors Responsible for the Regressive Alterations of the Kidney Parenchyma in Bright's Disease, The Pattern of the Kidney in Bright's Disease and Epicrisis and Prolegomenon. The discussions are accompanied by fine illustrations, including excellent photomicrographs showing sections and nephron dissections of diseased kidneys. The dissections present the third dimensional aspect of the diseased renal parenchyma. This is particularly well presented and represents many tedious and careful dissections by the author and his assistants. By such means the entire renal functioning unit, the nephron, was isolated and the architectural derangement associated with a particular type of renal disease located and visualized in the third dimension. The dissections are not limited to the glomeruli and tubules of the nephron, but include also the vascular structures supplying it. These studies are especially interesting in connection with the vascular types of renal disease. The book is appended by twenty-three plates of a hundred and fifty-five figures of nephron dissections. These are briefly and well supplemented by legends which point out the anatomic abnormalities. There are also sixteen stereograms by which the reader may see these kidney structures in the third dimension.

The book is lucidly written and includes important necropsy material that has been collected and admirably correlated. The reviewer was impressed by the lack of sufficient correlation between the anatomic disturbances and physiologic changes encountered in Bright's disease. Although such a presentation was beyond the scope of the book, discussions of that nature would probably have increased its values. The book is recommended to all in the various fields of medicine but particularly to pathologists and internists who need to think of diseased structures, not only renal, in the third dimension.

Consolidated Indices Compiled under the direction of the Publication Committee and the Editorial Office of the American Roentgen Ray Society. Price \$12.50. Pp 451. Springfield, Ill. Charles C. Thomas, Publisher, 1939.

The "Consolidated Indices" consists of a comprehensive index covering 160,000 references and 22,500 author references from the 30,000 pages of the four periodicals of the American Roentgen Ray Society. Under the chairmanship of Dr. Merrill C. Sosman, the publication committee, in collaboration with the editorial office, began early in 1936 to formulate plans for a complete subject and author index covering this entire group of publications. Dr. George H. Smith dealt with this mass of material. In the results of his compilation are seen a praiseworthy accomplishment.

In the "Indices" the transactions of the society, the original articles, the editorials and the biographic and historical sketches, together with the abstracts of both domestic and foreign journals, have been carefully and thoroughly indexed with regard both to subjects and to authors.

Included in this series, covering a period of approximately thirty-five years, are the *Transactions of the American Roentgen Ray Society* for the years 1903 to 1908, inclusive, the *American Quarterly of Roentgenology*, which in some measure overlapped the *Transactions*, being issued during the interval from 1906 and 1907 to 1912 and 1913, the *American Journal of Roentgenology*, comprising nine consecutive volumes issued from 1913-1914 through 1922, and the *American Journal of Roentgenology and Radium Therapy*, volumes X to XXXVIII, inclusive, the last completing the year 1937.

Dr. Smith explains the variations in the system of pagination occurring in these several publications and the significant errata. He explains the arrangement and presentation of the author and subject index, facilitating its use.

This work is a special event in publishing in this field of medicine.

The American Roentgen Ray Society presents a subject and author index to the medical world covering all of its publications. The Consolidated Indices will

be appreciated by every one as a convenient comprehensive reference source to most of the world roentgenologic and radium literature published from 1903 to 1937 inclusive

Die Diät-und Insulinbehandlung der Zuckerkrankheit By Dr Franz Depisch Second edition Price 4 80 marks Pp 155 Vienna Julius Springer, 1939

This treatise on the theory and treatment of diabetes is written for the German general practitioner. The second edition contains directions for the use of various types of long-acting insulins, such as protamine zinc insulin. The increasing incidence of diabetes has prompted the author to include a discussion of prevention, and since prevention can largely be effected by control of overweight, directions are given for reducing procedures.

The author regards diabetes as a disturbance of the normal balance between the activity of the islands of Langerhans and the opposing regulation of the blood sugar (*Gegenregulation*). The cause of diabetes in the great majority of cases, perhaps in all cases he says, depends on a certain functional insufficiency of the insular organ, but the clinical features of the individual case are determined not alone by the degree of insufficiency of the insular organ but also importantly by the associated state of activity of the opposing regulation.

For purposes of treatment, distinction is made between supportive management directed at the insufficiency of the islands of Langerhans and attempts to suppress the activity of the opposing regulation. The islands are spared by restricting the supply of sugar formers (carbohydrate and protein). This, however, depends on providing calories in the forms of fat which has the disadvantage, according to the author's view, of activating the opposing regulation. This disadvantage, as a rule, is balanced by the increasing capacity of the islands. The treatment directed at the opposing regulation involves the use of a liberal amount of carbohydrate and restriction of fat.

The book also contains much advice regarding the treatment of both the acute and the chronic complications of diabetes.

Etude morphologique et biologique sur les flagellés intestinaux parasites des murides Etude comparative des flagellés du cobaye By Leon Morenas Price, 60 francs, paper Pp 234 Paris Masson & Cie, 1938

This is a report of a thorough investigation of the flagellated intestinal parasites of wild and tame rats and mice and of guinea pigs. In these animals in a wild state infestation is usually of a single strain, while laboratory stocks generally harbor several strains. Of the flagellates studied, only *Giardia* appears to be pathogenic, the others could be considered commensals. The biologic experiments are interesting. It is apparent that the character and the quantity of intestinal mucus are determining factors in the selection of the sites of infestation. A predominantly gram-positive intestinal bacterial flora is unfavorable for parasitism. The effect of the avitaminoses studied is surprising. Scorbutic guinea pigs are neither more nor less susceptible to parasitic infestation than normal animals. Animals suffering from A-avitaminosis, however, because of the diminished production of mucus, are much more resistant to parasitism than are normal animals.

Efforts to produce animal infestation with human flagellates were not successful and suggested that the organisms are species specific and further that these animals are probably not vectors. The study is well done and should be a useful addition to the library of parasitologists.

SIGNIFICANCE OF THE ALBUMIN-GLOBULIN RATIO OF SERUM

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On the basis of solubility measurements, Sørensen¹ postulated that certain soluble proteins, including serum albumin and serum globulin, are not chemical entities but exist as a system of reversibly dissociable components held together by secondary valence forces. Recent investigations, following this lead, have thrown much doubt on the significance of the albumin-globulin ratio as employed in clinical practice. Ultracentrifugal studies² have indicated that a sensitive equilibrium exists between the molecular species constituting the serum protein complex. Thus, the ratio of small molecules to large molecules in a single sample of serum can be changed by aging, by simple dilution with water or Ringer's solution^{2a} and even by the presence of other protein molecules in the solution^{2b}. Although normal native serum appears to contain three molecular species and additional dispersion states are evident in pathologic serums, these in no way correspond with the albumin and globulin fractions obtained by "salting out"³. A marked interaction between the component proteins appears to take place readily, so that slight environmental changes cause large variations in the proportion

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1 Sørensen, S. P. L. The Constitution of Soluble Proteins, *Compt rend d trav du lab Carlsberg* **18** 1, 1930

2 (a) von Mutzenbecher, P. Dissoziationen und Assoziationen der Serum-moleküle, *Biochem Ztschr* **266** 259, 1933. (b) Pedersen, K. O. Ultracentrifugal Studies on Protein Mixtures, *Compt rend d trav du lab Carlsberg, serie physiol* **22** 427, 1938. (c) McFarlane, A. S. An Ultracentrifugal Investigation of the Serum Proteins, *Biochem J* **29** 407 (Feb) 1935, (d) The Ultracentrifugal Protein Sedimentation Diagram of Normal Human, Cow and Horse Serum, *ibid* **29** 660 (March) 1935, (e) The Behavior of Pathological Sera in the Ultracentrifuge, *ibid* **29** 1175 (May) 1935

3 McFarlane (footnote 2 c, d and e)

of one species to another. Measurements of the migration of serum protein molecules in an electric field (electrophoresis) have also demonstrated⁴ that preparations obtained by the customary salting-out procedures are not homogeneous but contain other fractions which can be isolated in the chambers of the apparatus. Observations of maximal, rather than final, colloid osmotic pressure values for samples of serum⁵ are in accordance with the total protein content but not with the albumin-globulin ratio. Agreement was obtained with the values predictable from the amounts of the two protein fractions present only after measurement of the "equilibrium" oncotic pressure after twenty-four hours. However, it was possible to obtain osmotic pressure curves with normal serums indistinguishable from those of hypoproteinemic serums over the entire twenty-four hour period by simple dilution of the former with saline solution. The reverse was also obtained experimentally. Chemical evidence supporting the view that the salted-out albumin and globulin fractions are artefacts has been obtained from amino acid analyses of such fractions⁶. The fractionation of serum by increasing concentrations of neutral salts yielded albumins and globulins of differing basic amino acid composition. However, despite variations in the ratio of these two fractions in a number of serums, the basic amino acid composition of the total coagulable protein in each case was found to be constant.

These studies have led to the "orosin" hypothesis,⁷ which postulates that the serum protein complex is composed of two or more unstable coprecipitation systems in mutual equilibrium. Variations in concentration of the isolated protein fractions, i. e., in the albumin-globulin ratio, are believed to result from environmental disturbances in the normal balance between the component systems before the electrolytes were introduced.

In the present study this hypothesis was investigated experimentally. Normal and hypoproteinemic serums were exposed simultaneously to the influence of the same environmental conditions by dialysis of one against the other for variable periods prior to addition of the salting-out reagent. In this way it was believed possible to determine the influence of variations in environmental conditions on the albumin-globulin ratios previously found to be characteristic of such serums.

4 Tiselius, A. Electrophoresis of Serum Globulin. II. Electrophoretic Analysis of Normal and Immune Serum, *Biochem J* **31** 1464 (Sept.) 1937.

5 Yanagi, K. A Clinical and Experimental Study of the Stability of Colloid Osmotic Pressure of Serum Protein, *J Clin Investigation* **14** 853 (Nov.) 1935.

6 Block, R. J. The Basic Amino Acids of Serum Proteins, *J Biol Chem* **103** 261 (Nov.) 1933.

7 Block, R. J. Proteins of the Nervous System Considered in the Light of the Prevailing Hypotheses on Protein Structure, *Yale J Biol & Med* **9** 445 (May) 1937.

EXPERIMENTAL METHOD AND RESULTS

Howe's method,⁸ employing a 1:2 solution of potassium dihydrogen phosphate (KH_2PO_4) and potassium phosphate (K_2HPO_4) to precipitate the globulin, was used throughout this study. This procedure gives essentially the same results as the sodium sulfate (Na_2SO_4) salting-out method but is more reproducible from day to day.⁹

Influence of Simple Dilution and Incubation on the Salting-Out Properties of the Serum Protein Complex—Serums from 3 normal persons were diluted with an equal volume of 0.9 per cent saline solution and immersed in a water bath at 37°C for twenty-four hours. A few small crystals of thymol were added as a preservative.¹⁰ The results, summarized in table 1, indicate that dilution of the normal concentration of serum protein to the hypoproteinemic level and subsequent incubation at body temperature do not cause a decrease in the albumin-globulin ratio, characteristic of hypoproteinemic serums.

TABLE 1—*Stability of the Albumin-Globulin Ratio of Normal Serums Diluted with an Equal Volume of Physiologic Solution of Sodium Chloride and Maintained at 37°C for Twenty-Four Hours*

Sample	Serum	Protein Concentration*			Albumin-Globulin Ratio
		Total, per Cent	Albu min, per Cent	Globu lin, per Cent	
A	Control, undiluted	6.37	4.81	1.56	3.08
	Experimental	3.19†	2.36	0.83	2.85
B	Control, undiluted	7.90	5.40	2.50	2.16
	Experimental	3.95†	2.63	1.27	2.10
C	Control, undiluted	7.54	4.99	2.55	1.96
	Experimental	3.77†	2.52	1.25	2.01

* In the calculation of the protein concentration in these normal serums the value for nonprotein nitrogen was considered to be 35 mg per hundred cubic centimeters.

† Calculated values.

Dialysis of Normal Versus Hypoproteinemic Serums—For the dialysis experiments several units of the apparatus sketched in the accompanying diagram were used. The diagram is self explanatory. Cellophane was used as the semipermeable membrane.¹¹ Markedly hypoproteinemic serums with low albumin-globulin ratios

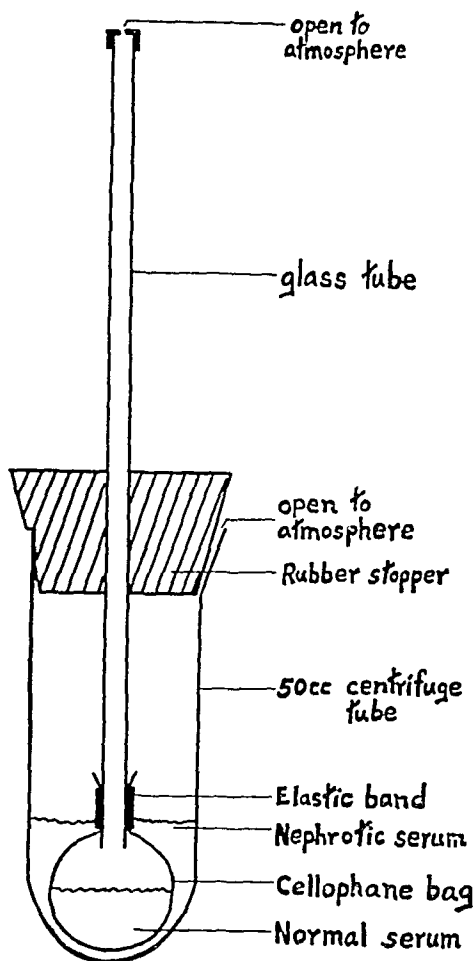
8 Howe, P. E. The Relative Precipitating Capacity of Certain Salts When Applied to Blood Serum or Plasma and the Influence of the Cation in the Precipitation of Proteins, *J. Biol. Chem.* **57**: 241 (Aug.) 1923.

9 The salting out of the globulin fraction from each sample of serum was carried out in duplicate. The average deviation of a single albumin determination from the average value obtained with each sample tested was ± 10 per cent, with a maximal deviation of ± 20 per cent. Total nitrogen minus nonprotein nitrogen was multiplied by 6.25 to obtain the value for protein.

10 Control determinations have indicated that this preservative exerts no effect on the salting-out properties of the serum protein complex.

11 Cellophane no. 300, furnished by E. I. du Pont de Nemours and Company, Wilmington, was used. It is impermeable to protein (Laviets, P. H. Anaerobic Ultrafiltration, *J. Biol. Chem.* **120**: 267 [Aug.] 1937; Yanagi⁵).

were obtained from patients in the nephrotic stage of glomerulotubular nephritis. By dialyzing such serum against normal serum it is possible to subject the serum protein complex in each sample to the same environmental influences. Water will leave the hypoproteinemic serum to dilute the normal sample. The temperature of both of the serums and, at equilibrium, the protein concentration, p_H and concentration of the plasma crystalloids will be the same. The serum proteins, however, cannot pass from one compartment to the other. If the "orosin" hypothesis⁷ is correct, the ratios of albumin to globulin on each side of the cellophane membrane should change from the original values and tend to approximate each other.



Unit used for the dialysis of normal against nephrotic serum

A typical series of experiments is described. Confirmatory results were derived from tests with normal and nephrotic serums obtained from other persons.

The dialysis experiments were conducted at first at 4 C in order to minimize bacterial contamination. The serums were collected and the experiments set up with aseptic precautions. Because of the low temperature of incubation no thymol was added as preservative. The results of these tests are presented in table 2. In both control serums, nephrotic and normal, incubated under the same conditions, there were no changes in the salting-out behavior of the serum protein complex. As a result of the dialysis the protein concentrations in both serums approached each other, the other environmental factors likewise tending to equilibrate them-

selves on each side of the membrane. However, the albumin-globulin ratios did not change.

The lack of appreciable change in the albumin-globulin ratio might have been due to inhibition of the association and dissociation of the serum protein molecules by the low temperature of incubation. Accordingly, aliquots of the same samples of serum previously dialyzed one against the other were maintained at 56°C for a three hour period. At this temperature the possibility of bacterial contamination is negligible, therefore no preservative was used. If the molecular changes in the serum protein molecules are chemical, the elevated temperature may be expected to promote such changes more readily. Indeed, incubation of serum at 56°C has been reported¹² to cause a transformation of serum albumin into serum globulin. Table 3 gives the results of these tests.

A definite change in the salting-out properties of the serum protein complex was observed. In all cases the albumin-globulin ratios were markedly less than the initial values (table 2). These results, however, do not indicate any change of

TABLE 2—*Stability of the Albumin-Globulin Ratio of Normal and Nephrotic Serums Maintained at 4°C and Dialyzed One Against the Other*

Serum	Protein Concentration*			Albumin-Globulin Ratio
	Total, per Cent	Albumin, per Cent	Globulin, per Cent	
Normal (immediate analyses)	7.42	5.06	2.36	2.14
48 hours at 4°C (control, without dialysis)	7.22	4.90	2.32	2.12
120 hours at 4°C (control, without dialysis)	7.30	4.93	2.37	2.08
Nephrotic (immediate analyses)	3.21	0.86	2.35	0.37
48 hours at 4°C (control, without dialysis)	3.15	0.76	2.39	0.32
120 hours at 4°C (control, without dialysis)	3.17	0.92	2.25	0.41
Normal (3 cc) dialyzed against nephrotic (7 cc)				
Normal 48 hours at 4°C (4.6 cc)	4.79	3.42	1.37	2.50
120 hours at 4°C (4.7 cc)	4.63	3.03	1.55	1.99
Nephrotic 48 hours at 4°C (5.7 cc)	3.55	0.85	2.70	0.32
120 hours at 4°C (5.6 cc)	4.06	1.10	2.96	0.37

* The value for nonprotein nitrogen was considered to be 35 mg per hundred cubic centimeters in each case.

albumin to globulin. If this transformation were possible, the ratio of the fractions in the dialyzed sample of normal serum in which environmental factors may have been expected to favor such a change should have been much less than that in the control. This was not the case. Furthermore, the dialyzed sample of nephrotic serum, in a position presumably favoring an increase in the albumin-globulin ratio, likewise showed a decrease in this ratio. The changes observed in these serums are attributed to incipient denaturation of the serum proteins. The globulin fraction is salted out in either case, but in the second instance, in addition, the partially denatured albumin fraction is also precipitated. That denaturation can occur without precipitation is indicated from analyses of four normal serums, the results are summarized in table 4. In these tests the only change observed

12. Moll, L. Ueber künstliche Umwandlung von Albumin in Globulin, Beitr. z. chem. Physiol. u. Path. **4**: 563 (Nov.) 1903. Rusznyak, S. Physikalisch-chemische Untersuchungen an Körperflüssigkeiten. VII. Die Umwandlung von Albumin in Globulin, Biochem. Ztschr. **140**: 179, 1923. Desbordes, J. Notion d'exsudat et de transsudat dans les liquides d'épanchement. Signification du rapport sérine/globuline, Compt. rend. Soc. de biol. **127**: 784, 1938.

during the heating of the samples of diluted serum at 100 C was the appearance of a slight opalescence. The normal p_H of serum is sufficiently removed from the isoelectric point of the proteins so that heat coagulation does not occur. Despite the fact that no visible precipitate formed, all the serum albumin was denatured and was salted out with the globulin fraction. Incipient denaturation of serum albumin comparable to that described in the present report may be the factor primarily responsible for the alleged conversion of albumin to globulin which has been reported in many papers¹³

TABLE 3—*Effect of Heating on the Albumin-Globulin Ratio of Normal and Nephrotic Serums Previously Maintained at 4 C and Dialyzed One Against the Other*

Serum	Protein Concentration*			Albumin Globulin Ratio
	Total, per Cent	Albumin, per Cent	Globulin, per Cent	
Normal 140 hours at 4 C, then heated 3 hours at 56 C (control without dialysis)	7.22	3.28	3.94	0.83
Nephrotic treated as above (control without dialysis)	3.13	0.36	2.77	0.13
Normal (3 cc) dialyzed against nephrotic (7 cc) 140 hours at 4 C, then heated 3 hours at 56 C				
Normal (4.7 cc)	4.48	2.32	2.16	1.08
Nephrotic (5.6 cc)	4.07	0.51	3.56	0.14

* The value for nonprotein nitrogen was considered to be 35 mg per hundred cubic centimeters in each case.

TABLE 4—*Albumin-Globulin Ratio of Serum Diluted with Physiologic Solution of Sodium Chloride (1:10) and Heated at 100 C for Five Minutes*

Serum Sample	Initial Protein Concentration*			Albumin Globulin Ratio	Albumin Concentration after Heat Treatment	
	Total, per Cent	Albumin, per Cent	Globulin, per Cent		Kjeldahl Determination, per Cent	Result of Protein Test†
A	6.37	4.81	1.56	3.08	0.0	Negative
R	7.90	5.40	2.50	2.16	0.0	Negative
M	7.56	4.87	2.69	1.81		Negative
P	7.42	5.06	2.36	2.14		Negative

* The value for nonprotein nitrogen was considered to be 35 mg per hundred cubic centimeters in each case.

† Sulfosalicylic acid (20% solution) was added to the filtrate after the salting out of the globulin fraction.

13 (a) Herzfeld, E, and Klinger, R. Studien zur Chemie der Eiweisskörper I. Die Eiweissfraction des Blutplasmas, II. Zur Theorie der Bakterien-Agglutination, *Biochem Ztschr* **83** 228, 1917. (b) Fischer, A. Antiprophthrombin und Globuline, *ibid* **244** 464, 1932. (c) Wu, H. Effect of Removal of Lipoid on Precipitability of Serum Proteins by Neutral Salts, *Chinese J Physiol* **7** 125 (July) 1933. (d) Kozawa, S, Iwatsuru, R, and Adachi, T. Studien über Harn-eiweiss, *Biochem Ztschr* **260** 313, 1933. (e) Hadaček, J. Albumins and Globulins in Blood Serum, *Časop lek česk* **17** 96, 1937, abstracted, *Chem Abstr* **31** 5823 (Aug) 1937. (f) Footnote 12.

Tests were carried out with aliquots of the same serums but with the dialysis continued at body temperature. A few small crystals of thymol were added as a preservative. The results are presented in table 5. In this experiment true equilibrium was attained, the concentrations of protein on both sides of the membrane being equal. Despite this the albumin-globulin ratios of both serums were the same as those of the controls without dialysis. Denaturation of the proteins in these tests was negligible. In the confirmatory tests with normal and nephrotic serums obtained from other persons the dialysis was allowed to proceed for forty hours at 37 C throughout. No evidence of protein denaturation was observed in these serums.

Influence of Serum Lipids on the Salting-Out Behavior of Serum Proteins—The serum lipids do not dialyze through the cellophane membrane¹⁴. However, the addition of these lipids to serum to yield clear solutions does not affect the precipitation limits of the proteins¹⁵. In the present study the serum lipids from nephrotic serums were isolated¹⁶ and added to physiologic solution of sodium

TABLE 5—*Effect of Body Temperature on the Albumin-Globulin Ratio of Normal and Nephrotic Serums Maintained Previously at 4 C and Dialyzed One Against the Other*

Serum	Protein Concentration*			Albumin Globulin Ratio
	Total, per Cent	Albu- min, per Cent	Glo- bu- lin, per Cent	
Normal 155 hours at 4 C, then heated 15 hours at 37 C (control without dialysis)	7.16	4.64	2.52	1.84
Nephrotic treated as above (control without dialysis)	3.17	0.59	2.58	0.23
Normal (3 cc) dialyzed against nephrotic (7 cc) 155 hours at 4 C and then 15 hours at 37 C				
Normal (5.4 cc)	4.33	2.88	1.45	1.99
Nephrotic (4.9 cc)	4.36	0.85	3.51	0.24

* The value for nonprotein nitrogen was considered to be 35 mg per hundred cubic centimeters in each case.

chloride. The suspension was then used to dilute normal serums (1:2), and the "solution" was incubated at body temperature for forty hours. No change in the albumin-globulin ratio was found.

Influence of Urinary Constituents On the Salting-Out Behavior of Serum Proteins—From the basic amino acid analysis of urinary protein, Block and his associates¹⁷ have concluded that urinary protein is not nearly all albumin but is total serum protein. Determinations conducted by Kozawa and his associates^{18a} with freshly voided urinary protein gave an albumin-globulin ratio of approximately 5:1. A repetition of these tests on the same samples of urine after dialysis and

14 Laviertes, P. H. Anaerobic Ultrafiltration, *J Biol Chem* **120** 267 (Aug) 1937.

15 Theorell, H. Studien über die Plasmaplipide des Blutes, *Biochem Ztschr* **223** 1, 1930.

16 Sørensen¹ Wu^{18c}

17 Block, R. J., Darrow, D. C., and Cary, M. K. The Basic Amino Acids of Serum Proteins. III. A Chemical Relationship Between Serum Proteins of Various Origins, *J Biol Chem* **104** 347 (Feb) 1934.

concentration to simulate conditions in the serum yielded values approximating 1.1. These were identical with the ratios obtained with serums from the same patients. These experiments have led to the conclusion that urinary protein is total serum protein but that because of the influence of the environmental factors, including the well known solvent action of urea solutions for protein, it is salted out like serum albumin. However, in these tests ample opportunities for incipient denaturation of the urinary protein during dialysis and concentration were present, so that the decrease noted in the albumin-globulin ratio may have been due entirely to such a factor. If urinary constituents modify the salting-out behavior of the protein excreted, the addition of serum to urine should result in an increase in the albumin-globulin ratio, giving one characteristic of urinary proteins.

One cubic centimeter samples of normal and nephrotic serums were added to 9 cc samples of urine collected from these persons. The serums and urines were also crossed so that normal serums in pathologic urine were obtained, and vice versa. After a twenty-four hour incubation period at 37 C the samples were tested to determine whether any change occurred as compared with the initial albumin-globulin ratios of the serums.

In these tests the globulin fraction was estimated nephelometrically rather than by the conventional Kjeldahl nitrogen determination. The level of nonprotein nitrogen in the urine filtrate, subsequent to salting out, is relatively high in relation to that of albumin nitrogen, so that a small error in the determination can markedly alter the value obtained for the protein. The turbidity obtained when the salting-out reagent was added to the sample of serum diluted with urine and subsequently incubated was compared immediately with that obtained with the same serums diluted with saline solution. The readings were made before flocculation of the globulin particles occurred. This method has been tested for reproducibility and with varying quantities of serum, the results are believed to be accurate to within ± 10 per cent¹⁸. Such a degree of accuracy is satisfactory for the purpose of this investigation. In all cases the turbidities due to the globulin fraction, salted out after the period of incubation, were the same regardless of whether saline solution or urine was used as the diluent. No evidence of denaturation of the serum proteins, judging from their salting-out behavior, was noted in the control tests. These experiments seem to indicate that urinary protein is not total serum protein but is derived principally from the albumin fraction.

COMMENT

The constancy of the albumin-globulin ratio in the present studies does not support the "orosin" hypothesis.⁷ Normal and hypoproteinemic serums when subjected to the same environmental influences still give the same initial albumin-globulin ratios characteristic of such serums. These findings do not indicate that native serum contains discrete proteins identical with those salted out. It is our opinion that the dissociation and association reactions of the serum protein complex, which are responsible for the sensitive equilibrium between the molecular species in native serum, must occur within independent systems. On the addition of the salting-out reagent the components in each of these

¹⁸ A method based on the same principle but using a different salting-out reagent has recently been described (Paic, M. M., and Deutsch, V. *Microdosage colorimetrique des globulines*, *Bull. Soc. chim. biol.* **20** 1112 [Sept.-Oct.] 1938).

systems combine, probably by means of residual valencies, into a product that is insoluble under the imposed conditions. Likewise, it should be emphasized that the ultracentrifugal technic measures simply the number of dispersion states in which the serum protein complex exists and the relative concentrations associated with them. The chemical identities of the molecular species are not determined.

When serum is diluted with physiologic solution of sodium chloride, there is a marked fall of specific osmotic pressure of the serum protein as estimated from the stable readings taken after twenty-four hours or longer.¹⁹ This effect has been shown in the present study not to be due to any change of albumin to globulin. It has been attributed by Peters and Van Slyke²⁰ to the appreciable volume of the proteins. However, measurements²¹ of the specific apparent volume of serum albumin and serum globulin in aqueous solution and in plasma do not seem to support such an explanation. The most plausible explanation is derived from ultracentrifugal studies²² of artificial mixtures of the molecular species in native serum, the proteins of smaller molecular size on dilution associate to form larger molecules, and, since osmotic pressure varies inversely with the molecular weight, there is accordingly a decrease in the specific oncotic pressure of serum protein. This disproportion between the oncotic pressure and the protein concentration, however, is not manifest in the values for maximal colloid osmotic pressure obtained at the end of the sixth to the seventh hour.⁵ This is strongly suggestive that some change in the serum protein complex (association into the larger molecular species) occurs several hours after the serum is placed in the osmometer. Thus, colloid osmotic pressure measurements in vitro may not represent the true state of affairs as they exist in the plasma.

As the albumin-globulin ratio, determined by salting-out procedures, does not reflect the dispersion state of the serum protein or the relative amounts of the molecular species in any given serum,

19 Verney, E. B. The Osmotic Pressure of the Proteins of Human Serum and Plasma, *J. Physiol.* **61** 319 (June) 1926. Fishberg, E. H. The Relations of the Serum Proteins and Lipids to the Osmotic Pressure, *J. Biol. Chem.* **81** 205 (Jan.) 1929. Kylin, E. Studien über den kolloid-osmotischen (onkotischen) Druck, *Ztschr. f. d. ges. exper. Med.* **93** 480 (April) 1934. Gronwall, A. Ueber die Bedeutung des Verhältnisses zwischen Bluteiweisskonzentration und dem sogenannten kolloidosmotischen Druck, *Biochem. Ztschr.* **276** 223, 1935. Yanagi.⁵

20 Peters, J. P., and Van Slyke, D. D. Quantitative Clinical Chemistry I Interpretations, Baltimore, Williams & Wilkins Company, 1932.

21 Svedberg, T., and Sjogren, B. The Molecular Weights of Serum Albumin and of Serum Globulin, *J. Am. Chem. Soc.* **50** 3318 (Dec.) 1928. Oberst, F. W. Specific Volume of Plasma and Serum Proteins in Pregnant and in Parturient Women and Their Newborn Children as Derived from Viscosity Measurements, *J. Clin. Investigation* **18** 799 (Nov.) 1939.

determinations of the ratio seem to have little value in predicting the true oncotic pressure in vivo. Furthermore, to attribute to the albumin fraction (estimated by salting out) major importance in preventing the passage of the fluids of plasma across the wall of the capillary into the tissues does not seem valid in the light of the recent physicochemical studies of the serum protein complex.

It is probable that changes in the serum protein dispersion state may occur in vivo comparable to those observed in the ultracentrifuge, with corresponding changes in oncotic pressure but not in the albumin-globulin ratios. In dogs subjected to prolonged plasmapheresis (experimental plasma depletion) there is a reduction in the serum protein concentration, with a corresponding decrease in the albumin-globulin ratio.²² In comparable experiments²³ it was found that the parallelism between change in plasma volume and change in serum protein concentration could be disturbed by a significant decrease in the volume of red cells. Under such circumstances the plasma volume may actually be greater than the initial normal value despite the hypoproteinemia and the decreased albumin-globulin ratio. An alteration in the serum protein dispersion state resulting in an increase in the smaller molecular species can account for this. The reverse may also take place in vivo. Dogs subjected to prolonged plasmapheresis will become edematous much more easily when large quantities of saline solution are given orally or parenterally.²⁴ However, despite the formation of edema by such an experimental procedure, neither the total serum protein concentration nor the albumin-globulin ratio is markedly affected when compared with the values for the same dog during the preceding hypoproteinemia without edema.²⁵ The animals, except for hypoproteinemia,

22 McNaught, J. B., Scott, V. C., Woods, F. M., and Whipple, G. H. Blood Plasma Protein Regeneration Controlled by Diet. Effects of Plant Proteins Compared with Animal Proteins, the Influence of Fasting and Infection, *J. Exper. Med.* **63** 277 (Feb.) 1936.

23 Melnick, D., and Cowgill, G. R. The Serum Protein Complex as a Factor in Regulating Blood Volume, *Proc. Soc. Exper. Biol. & Med.* **35** 312 (Nov.) 1936.

24 (a) Lestei, L. Experimental Nephrotic Edema, *Arch. Int. Med.* **48** 1 (July) 1931. (b) Barker, M. H., and Kirk, E. J. Experimental Edema (Nephrosis) in Dogs in Relation to Edema of Renal Origin in Patients, *ibid.* **45** 319 (March) 1930. (c) Darrow, D. C., Hopper, E. B., and Cary, M. K. Plasmapheresis Edema. I. The Relation of Reduction of Serum Proteins to Edema and the Pathological Anatomy Accompanying Plasmapheresis, *J. Clin. Investigation* **11** 683 (July) 1932.

25 (a) Shelburne, S. A., and Egloff, W. C. Experimental Edema, *Arch. Int. Med.* **48** 51 (July) 1931. (b) Lepore, M. J. Experimental Edema Produced by Plasma Protein Depletion, *ibid.* **50** 488 (Sept.) 1932. (c) Kirk, E. J. Studies of Edema, Especially the Edema of Renal Origin, *Am. J. Clin. Path.* **5** 21 (Jan.) 1935. Barker and Kirk^{24b} Darrow and others^{24c}

are normal and show no evidence of vascular permeability to protein or changes in blood pressure^{24a} The capillaries are permeable to salt solution in both directions, and the animals, as in most cases of edema in the human being, have no difficulty in excreting salts^{25b} Possibly in such conditions of hypoproteinemia with excessive intake of sodium chloride a decrease in the amount of the smaller molecular species in serum with a corresponding increase in the larger molecular forms occurs, a drop in the oncotic pressure *in vivo* would follow

Although the albumin globulin ratios as determined by salting-out procedures may not be indicators of the oncotic pressure *in vivo*, such ratios are not necessarily without significance The fact that they are altered in certain pathologic states and remain constant under the experimental conditions described here would seem to indicate that the ratios obtained are real and indicative of the relative amounts of these two independent protein systems in native serum Association and dissociation changes must occur within these independent systems

SUMMARY

The albumin-globulin ratios characteristic of normal and hypoproteinemic serums represent the relative amounts of two independent protein systems, which may be separated by salting-out procedures Dissociation and association phenomena attributed to the serum protein molecules must occur within these independent systems Exposing normal and hypoproteinemic serums to the same environmental factors by dialysis of one against the other does not alter the ratio of one protein fraction to another The influence of incipient denaturation on the salting-out behavior of the serum protein complex has been studied and serves to explain the alleged conversion of albumin to globulin reported by others Urinary protein does not represent total serum but is derived principally from the albumin fraction

The inadequacy of colloid osmotic pressure measurements *in vitro* and of the determinations of albumin and globulin for predicting the true oncotic pressure *in vivo* are discussed in the light of recent physico-chemical studies of the serum protein complex

A PRACTICAL METHOD FOR THE MEASUREMENT OF GLOMERULAR FILTRATION RATE (INULIN CLEARANCE)

WITH AN EVALUATION OF THE CLINICAL SIGNIFICANCE
OF THIS DETERMINATION

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AND
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The kidney, by virtue of its peculiar structure, lends itself particularly well to quantitative measurements. Until recently most studies concerning the quantitative aspects of renal function have dealt with the excretion of urea and exogenous creatinine. The extensive studies of Ambard,¹ Addis,² and Moller, McIntosh and Van Slyke³ have developed the laws governing the excretion of urea by the normal and the diseased human kidney. These studies have led to practical tests of renal function. Of these, the Ambard coefficient is now of historical interest only. The Addis urea ratio, though somewhat too complicated for routine use, is a good quantitative test of renal function. The urea clearance test of Van Slyke and his associates has been adopted universally as a simple and precise estimate of the functional state of the kidneys. Recent studies⁴ have shown that the excretion of urea depends on a balance between the glomerular filtration rate and tubular reabsorption.

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1 Ambard, L. Rapports entre le taux de l'urée dans le sang et l'élimination de l'urée dans l'urine, *Compt rend Soc de biol* **69** 411, 1910

2 Addis, T. The Ratio Between the Urea Content of the Urine and the Blood After the Administration of Large Quantities of Urea. An Approximate Index of the Quantity of Actively Functioning Kidney Tissue, *J Urol* **1** 263 (June) 1917

3 Moller, E., McIntosh, J. F., and Van Slyke, D. D. Studies of Urea Excretion. II. Relationship Between Urine Volume and the Rate of Urea Excretion by Normal Adults, *J Clin Investigation* **6** 427 (Dec) 1928

4 (a) Van Slyke, D. D., Hiller, A., and Miller, B. The Clearance, Extraction Percentage and Estimated Filtration of Sodium Ferrocyanide in the Mam-

(Footnote continued on next page)

During the past decade there has been a great advance in knowledge of the excretion characteristics of the human kidney, in large part due to the studies of Smith and Shannon and their associates⁵ It is now possible to make precise measurements of the glomerular filtration rate, the effective renal blood flow and the capacity of the tubular cells to reabsorb or excrete certain compounds Many of these measurements are too difficult at present for clinical purposes, but, as will be shown in this paper, one can measure the glomerular filtration rate rather simply with both normal and diseased persons by employing a simplified inulin clearance test

Inulin, a polysaccharide which is not metabolized by the body, has the unique distinction of being excreted consistently by glomerular filtration in the human kidney without tubular excretion or reabsorption⁶ If one considers the formula for the clearance, UV/B (U being the concentration of the excreted compound in the urine, B its concentration in the blood [or plasma] and V the flow of urine in cubic centimeters per minute), it can be seen that for such a compound as inulin the clearance is equal to the glomerular filtration rate In other words, the milligrams of inulin found per minute in the vesical urine are contained in that volume of plasma "cleared" per minute Since inulin is excreted only by filtration, the volume (in cubic centimeters) of plasma

malian Kidney Comparison with Inulin, Creatinine and Urea, *Am J Physiol* **113** 611 (Nov) 1935 (b) Gordon, W, Alving, A S, Kretzschmar, N R, and Alpert, L Variations in the Extraction of Urea by the Kidney and Their Relation to the Amount of Urea Reabsorbed, *ibid* **119** 483 (July) 1937 (c) Chassis, H, and Smith, H The Excretion of Urea in the Normal Man and in Patients with Glomerulonephritis, *J Clin Investigation* **17** 347 (May) 1938

5 (a) Smith, H W The Physiology of the Kidney, New York, Oxford University Press, 1937, Kidney, *Ann Rev Physiol* **1** 503, 1939, Studies in the Physiology of the Kidney, Publication of the University Extension Division, University of Kansas, Lawrence, Kan, 1939 (b) Shannon, J A Renal Tubular Excretion, *Physiol Rev* **19** 63 (Jan) 1939, (c) The Renal Excretion of Creatinine in Man, *J Clin Investigation* **14** 403 (July) 1935 (d) Smith, H W, Goldring, W, and Chassis, H The Measurement of the Tubular Excretory Mass, Effective Renal Blood Flow and Filtration Rate in the Normal Human Kidney, *ibid* **17** 263 (May) 1938 (e) Shannon, J A, and Fisher, S The Renal Tubular Reabsorption of Glucose in the Normal Dog, *Am J Physiol* **122** 765 (June) 1938 (f) Smith, H W, Goldring, W, Chassis, H, and Ranges, H A Observations on the Effective Renal Blood Flow and the Functional Excretory Mass in Man, with Special Reference to Essential Hypertension, *ibid* **123** 189 (July) 1938

6 Recent preliminary studies by Smith suggest that mannitol and solitol are excreted entirely by glomerular filtration (Smith, H W Studies in the Physiology of the Kidney, Publication of the University Extension Division, University of Kansas, Lawrence, Kan, 1939)

cleared must be equal to the volume of filtrate formed in the glomeruli per minute. This follows from the fact that inulin, being freely filtrable at the glomerulus, has essentially the same concentration in the protein-free glomerular filtrate as in the plasma.

The evidence that inulin clearance is an exact measure of glomerular filtration in the normal human being has been extensively reviewed by Smith.^{5a} Experiments recently performed by Miller, Alving and Rubin⁷ support the results of others for normal persons and add evidence for nephritic and hypertensive persons.

The clearances of other compounds than inulin have been proposed for clinical measurement of the glomerular filtration rate. Rehberg,⁸ the first investigator to attempt such measurements, employed the clearance of exogenous creatinine. That exogenous creatinine is excreted by the tubules as well as the glomeruli in man has been demonstrated clearly by Shannon.^{5c} Therefore it is apparent that the Rehberg clearance test should be abandoned as a clinical measure of the glomerular filtration rate. The situation with endogenous creatinine is more complex. Experiments with this compound⁹ indicate that endogenous creatinine may be excreted at the level of the filtration rate, but that in many normal and in most nephritic subjects the endogenous creatinine clearance is considerably higher than the inulin clearance. Despite these experiments, which were performed with a specific, enzymatic method for creatinine (Miller and Dubos¹⁰), several investigators¹¹ have advocated the endogenous creatinine clearance, as determined by nonspecific analytic methods, for clinical measurement of the glomerular filtration

7 Miller, B. F., Alving, A. S., and Rubin, J. The Renal Excretion of Inulin at Low Plasma Concentrations of This Compound, and Its Relationship to the Glomerular Filtration Rate in Normal, Nephritic and Hypertensive Individuals, *J. Clin. Investigation* **19**: 89 (Jan.) 1940.

8 Rehberg, P. B. Studies on Kidney Function. I. The Rate of Filtration and Reabsorption in the Human Kidney, *Biochem. J.* **20**: 447 (April) 1926.

9 (a) Miller, B. F., and Winkler, A. Renal Excretion of Endogenous Creatinine in Man. Comparison with Exogenous Creatinine and Inulin, *J. Clin. Investigation* **17**: 31 (Jan.) 1938. (b) Miller, B. F., Alving, A. S., Allinson, M. J. C., and Flox, J. Experiments, to be published.

10 Miller, B. F., and Dubos, R. Determination by a Specific, Enzymatic Method of the Creatinine Content of the Blood and Urine from Normal and Nephritic Individuals, *J. Biol. Chem.* **121**: 457 (Nov.) 1937.

11 (a) Popper, H., and Mandel, E. Filtrations- und Resorptionsleistung in der Nierenpathologie, *Ergebn. d. inn. Med. u. Kinderh.* **53**: 685, 1937. (b) Steinitz, K., and Turkand, H. The Determination of the Glomerular Filtration by the Endogenous Creatinine Clearance, *J. Clin. Investigation* **19**: 285 (March) 1940. (c) Arkin, A., and Popper, H. Urea Reabsorption and Relation Between Creatinine and Urea Clearance in Renal Disease, *Arch. Int. Med.* **65**: 627 (March) 1940.

rate in diseased as well as in normal kidneys. Until more is known of the excretion characteristics of endogenous creatinine it seems best not to employ this clearance as a measure of glomerular filtration rate.

Stieglitz and Knight¹² and recently Stieglitz¹³ have proposed the urinary excretion of sodium ferrocyanide as a test of the glomerular filtration rate. It is based on histochemical investigations by Gersh and Stieglitz,¹⁴ who demonstrated conclusively in the rabbit that ferrocyanide is excreted entirely by glomerular action. Later, Van Slyke, Hiller and Miller,¹⁵ by physiologic studies, showed that the clearance of sodium ferrocyanide in the dog is equal to the glomerular filtration rate. However, there are objections to the clinical application of the ferrocyanide excretion test. 1. Clearance studies with sodium ferrocyanide on normal human subjects performed by Miller and Winkler¹⁵ indicate that sodium ferrocyanide is reabsorbed in the human kidney. They found the ferrocyanide clearance to be about equal to the clearance of urea, which is both filtered and reabsorbed. Moreover, sodium ferrocyanide, in plasma concentrations comparable to those one can reasonably expect to be present in patients with low renal function during Stieglitz' test, caused considerable damage to the renal tubules. These observations strongly suggest that sodium ferrocyanide enters the tubules in man. 2. The ferrocyanide procedure is an excretion test, not a clearance test, and may give erroneous results because it does not take into account the concentration of the substance in the blood. Ferrocyanide is dissolved in the entire volume of extracellular fluid, of which the aqueous portion of the plasma constitutes only a small fraction. Therefore, changes in the volume of body fluid, by altering the concentration of ferrocyanide in the plasma, will affect the total urinary excretion of this compound. Because of these objections it is our opinion that ferrocyanide is unsuitable for the study of the glomerular filtration rate in man.

Of the several compounds proposed for measurement of the filtration rate in man only inulin appears to be satisfactory for clinical use. Measurements of inulin clearance until now have been restricted to research studies because of the absence of a suitable analytic technic. Previously it was usually necessary to inject large quantities of inulin

12 Stieglitz, E. J., and Knight, A. A. Sodium Ferrocyanide as a Clinical Test of Glomerular Efficiency. Preliminary Report, *J. A. M. A.* **103** 1760 (Dec 8) 1934.

13 Stieglitz, E. J. Test of Glomerular Function with Sodium Ferrocyanide. Further Studies, *Arch. Int. Med.* **64** 57 (July) 1939.

14 Gersh, I., and Stieglitz, E. J. Histochemical Studies on the Mammalian Kidney. I. The Glomerular Elimination of Ferrocyanide in the Rabbit, and Some Related Problems, *Anat. Rec.* **58** 349 (March) 1934.

15 Miller, B. F., and Winkler, A. W. The Ferrocyanide Clearance in Man, *J. Clin. Investigation* **15** 489 (Sept.) 1936.

to maintain the concentration at about 100 mg per hundred cubic centimeters of plasma. Recently, a very sensitive and relatively simple colorimetric method for inulin determination was developed by Alving, Rubin and Miller.¹⁶ By this procedure, inulin may be determined accurately at plasma concentrations as low as 5 mg per hundred cubic centimeters. Miller, Alving and Rubin⁷ showed that the inulin clearance at low plasma concentrations in normal, nephritic and hypertensive persons is an adequate measure of the glomerular filtration rate. By simplifying the procedure used by these authors we have been able to adapt the inulin clearance to practical clinical use and yet retain the accuracy that has been achieved previously in research studies. This paper presents the experimental background for the test and the technical details.

EXPERIMENTS

A study has been made of (a) the rate of fall in concentration of serum inulin after a single injection of 10 Gm of inulin and (b) the constancy of the values for inulin clearance obtained after the injection. Experiments were performed on 2 normal subjects and on 6 persons with nephritis or some other renal disease.

Procedure—The plan of the experiments and the technic employed were the same as have been reported in previous studies.⁷

Results—After intravenous injection of 10 Gm of inulin the plasma (or serum) concentration of inulin, plotted logarithmically against time, decreased at first in a curvilinear manner, later falling, however, in a linear or almost linear relation with time (charts 1 and 2). The curvilinear relation marks, presumably, the period of equilibration between the blood plasma and the extracellular fluid. The straight line relation follows because, once equilibrium has been established, the rate of fall of the level of plasma inulin is determined by the rate at which inulin is cleared from the plasma by the kidneys.

The mean concentration of plasma inulin for each period of collection of urine nearly equals the midpoint value¹⁷ when a straight line rela-

16 (a) Alving, A. S., Rubin, J., and Miller, B. F. A Direct Colorimetric Method for the Determination of Inulin in Blood and Urine, *J. Biol. Chem.* **127** 609 (March) 1939. (b) Alving, A. S., Miller, B. F., and Flox, J. Further Notes on the Colorimetric Determination of Inulin, to be published.

17 The true mean inulin plasma concentration for a given period of collection of urine is somewhat higher than the midpoint value. The mean concentration approaches the midpoint concentration as the period of urine collection is shortened. When periods of collection of urine are an hour or longer the mean concentration of inulin in the plasma may be represented by the level of inulin occurring in the

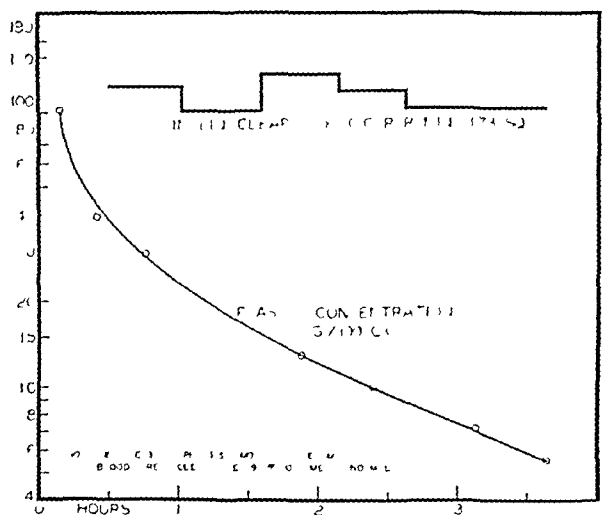
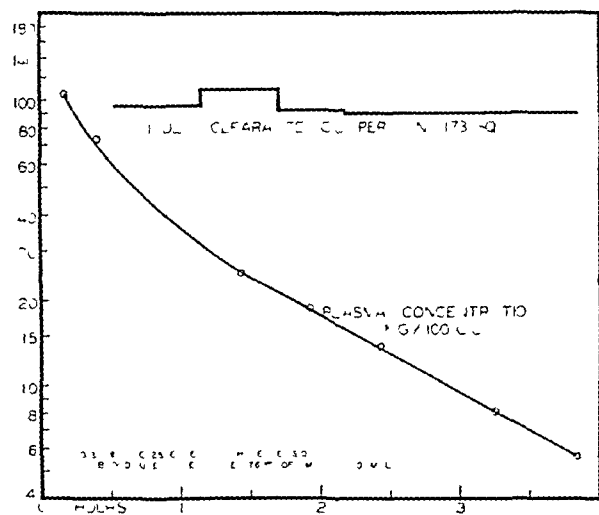
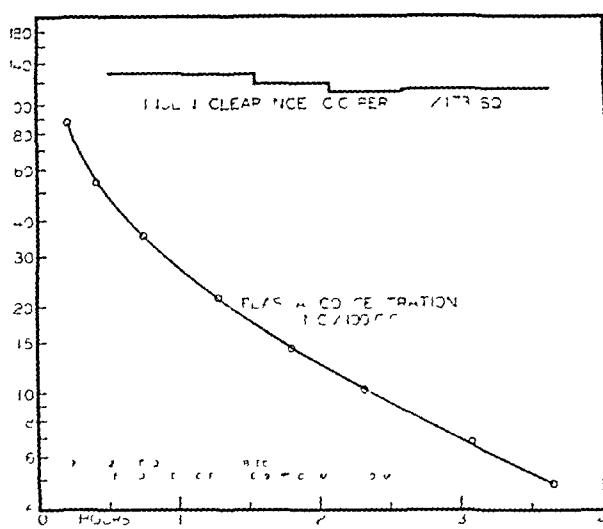
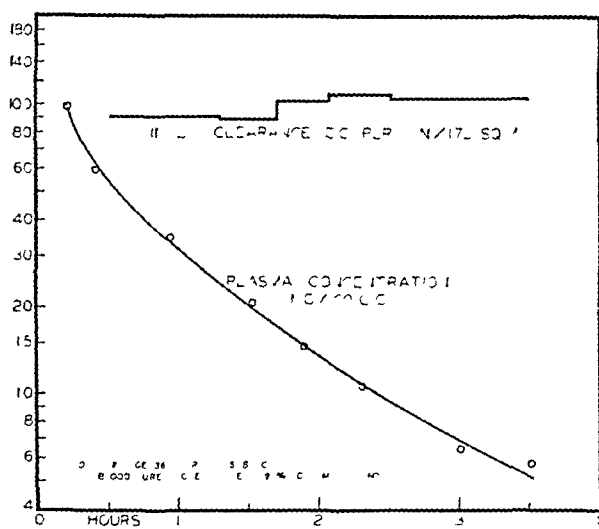


Chart 1—Inulin clearance and blood plasma concentration after intravenous injection of 10 Gm of inulin in persons with normal renal function

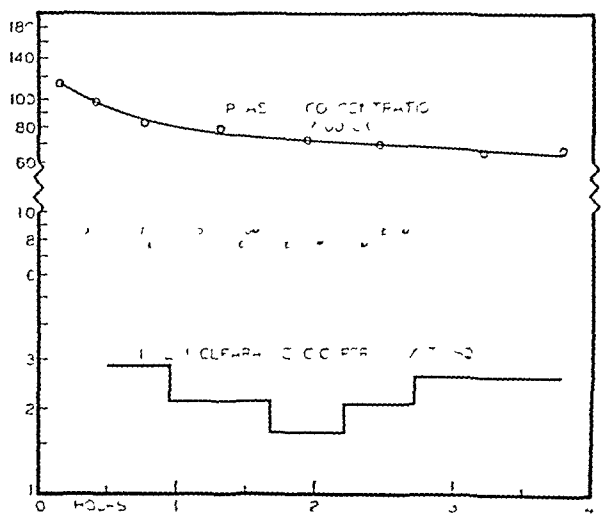
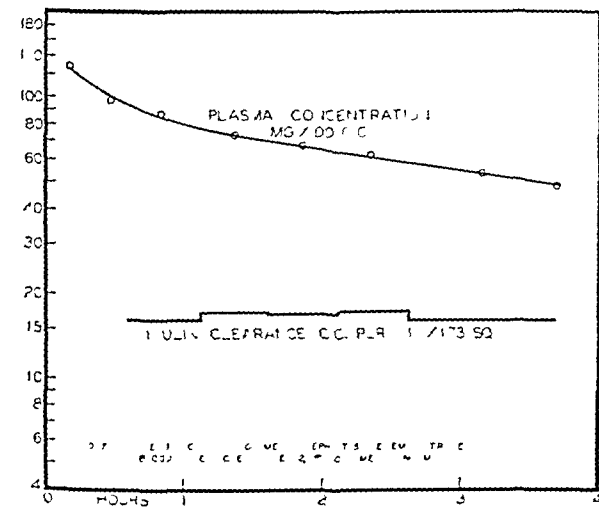
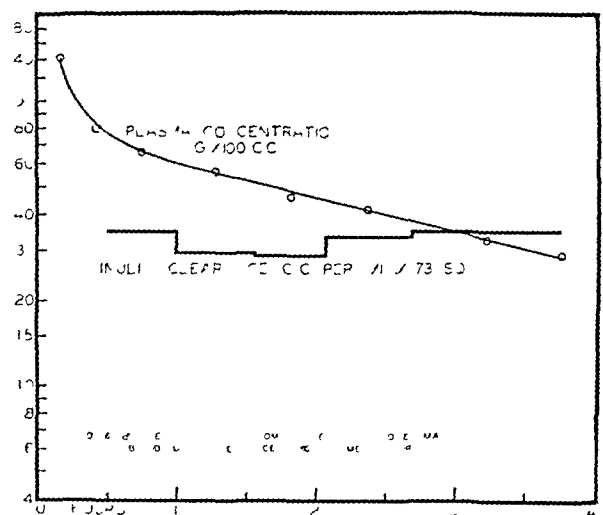
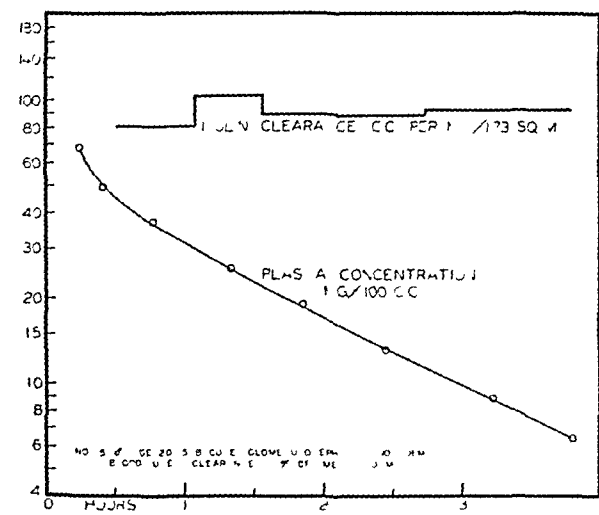


Chart 2—Inulin clearance and blood plasma concentration after intravenous injection of 10 Gm of inulin in patients with glomerulonephritis

tion exists. Therefore it is apparent that determinations of inulin clearance can be performed best after the initial period of equilibration.

The period of equilibration between the plasma and the tissues varies considerably from one person to another. It is usually complete in less than one hour, but in exceptional cases, such as those in which the subjects have a massive accumulation of fluid, the period of equilibration may last for one and one-half hours after intravenous injection of inulin.

In the charts the absolute values for inulin clearances are given. It is evident that the clearance values are independent of the concentration of inulin in the plasma, even at the very low levels. (More data on this point may be found in the paper of Miller, Alving and Rubin⁷.)

These results lead to the following conclusion. The clearance of plasma inulin may be measured accurately over a period of several hours after a single intravenous injection of a small quantity of inulin. In clinical tests, determination of the inulin clearance should be started one to one and one-half hours after injection of inulin. This interval gives satisfactory equilibration of inulin between the plasma and the extracellular fluid.

DESCRIPTION OF A SIMPLE CLINICAL PROCEDURE FOR MEASUREMENT OF THE GLOMERULAR FILTRATION RATE

By modification of the procedure just described, a simple test for routine clinical use has been developed. The routine test is performed best during two periods of collection of urine, one period serving as a check on the other. We perform the test as follows.

Preparation of the Subject—The inulin clearance test may be started at any time of the day, but whenever possible it should be done in the morning. It is best to keep the subject reclining during the test. His height and weight are recorded for calculation of the surface area.

plasma several minutes before the midpoint. For research purposes the correct mean concentration of inulin in the plasma may be determined by the following equation

$$C_M = \frac{C_1 - C_2}{2.303 \log C_1/C_2}$$

wherein

C_M = mean inulin concentration of the plasma during any period of collection of urine

and

C_1 and C_2 = inulin concentration of the plasma at the beginning and end, respectively, of the period of collection of urine

It is only necessary to obtain two blood samples at different times during the straight part of the plasma inulin curve to estimate the true mean concentration. The values of C_1 and C_2 may be determined graphically in a manner similar to that described under calculation of the midpoint plasma concentration. The inulin concentration in the blood falls so slowly after equilibrium has been reached that correction for "delay time"^{5d} is of no clinical significance except in special cases.

A light breakfast is given, usually consisting of one-half glass of milk and one slice of toast and butter (at 7 30 a m) Unless administration of fluid is contraindicated, it is desirable to promote a free flow of urine during the test For this purpose the subject is given one glass of water at 6 30 a m and every half hour thereafter until the test is finished

Control Samples of Blood and Urine—A sample of blood is always obtained before inulin is injected This sample serves to correct the subsequent analyses of blood inulin for the non-inulin chromogenic material The control sample is analyzed in the same manner as the blood containing inulin

A control sample of urine, on the other hand, is obtained only when it is necessary to achieve the greatest possible accuracy in testing patients with severely damaged kidneys In cases of uremia a maximum error of 10 per cent may be introduced by ignoring the non-inulin chromogenic material in the urine For ordinary clinical purposes the control sample of urine can be neglected even for uremic subjects For nonuremic subjects the error is always less than 1 per cent

Administration of Inulin—At 8 00 a m , 10 Gm of inulin¹⁸ dissolved in 100 cc of physiologic solution of sodium chloride is injected intravenously at a rate of 10 cc per minute The inulin solution should be brought to body temperature before injection¹⁹ (Any other time convenient to the individual clinician may be chosen for the intravenous injection, provided that the schedule of fluid administration is changed correspondingly)

Collection of Urine—If the flow of urine is very rapid or there is good reason to believe that emptying of the bladder is complete, catheterization is unnecessary Whenever possible, male patients should be

18 By employing the colorimetric method of Alving, Rubin and Miller¹⁶ for analysis of inulin, the clearances may be performed in the case of the normal adult after injection of as little as 5 Gm of inulin and in uremic patients after injection of a much smaller quantity We have chosen to inject 10 Gm, since this is the smallest quantity which will permit accurate analyses of the blood for several hours in persons with normal renal function and anasarca We prefer to dilute the serum filtrates rather than to change the dose of inulin for uremic patients Should it be desirable in research studies to perform clearance tests over a longer period than three and one-half hours, a larger quantity of inulin may be administered

19 Nontoxic sterile inulin may be obtained in ampules containing 5 Gm of inulin in 50 cc of physiologic solution of sodium chloride from the U S Standard Products Company, Woodworth, Wis Because the inulin tends to crystallize out of solution slowly at room temperature, the ampule should be placed in boiling water until the inulin redissolves The inulin should be shaken vigorously before heating In the case of solutions having excessive crystallization, the time necessary for redissolving the inulin may exceed one-half hour The solution should be perfectly clear before injection

allowed to void their urine in the standing position. When catheterization is necessary the bladder should be washed with three 20 cc portions of physiologic solution of sodium chloride. These washings are added to the urine and thoroughly mixed with it, this mixture is taken as the sample of urine for the period, and the inulin analyses and calculations of the urine flow are made from it. The end of the third washing of the bladder is recorded as the time of collection of urine.

The bladder is emptied one hour (or one and one-half hours in the case of a patient with massive edema) after completion of the injection of inulin, and this urine is discarded. Two consecutive hourly collections of urine are then made. The resulting samples of urine, which represent the collections for the clearance periods, are timed accurately, measured and analyzed for inulin.

It is not essential that the periods of collection of urine be exactly one hour. It is absolutely essential that the bladder be emptied completely each time and that the periods be timed accurately.

Collection of the Samples of Blood—At the midpoint of each clearance period (one and one-half and two and one-half hours after the end of the injection of inulin in patients without anasarca) 15 cc or more of blood is drawn by venipuncture. Every attempt should be made to collect the blood at the midpoint of each period of collection of urine, but even if the time does not correspond to the exact midpoint the proper value may be found, as will be shown later in the section on calculations.

Either blood serum or plasma (from oxalated or heparinized blood) may be employed for the analyses.

Analysis of Inulin in Blood and Urine—It is possible by reference to charts 1 and 2 to predict the approximate concentrations of blood inulin that will be found in the "midpoint samples." This concentration will depend on (a) the renal function, i. e., the higher the clearance, the lower the concentration of blood inulin and (b) the volume of extracellular fluid in which the inulin can diffuse, thus, for patients with anasarca the value for plasma inulin will be lower than for nonedematous persons with the same level of renal function.

In order to make the proper dilution of the urine, after a protein-free filtrate has been made, one approximates the concentration of inulin in the urine as follows. A fair guess as to the percentage of renal function can usually be made from knowledge of the clinical condition of the patient or from previous tests of renal function such as the blood urea clearance, urine concentrating ability or the phenolsulfonphthalein test. This percentage times 1.25 is assumed to be the inulin clearance for the subject. The approximate concentration of inulin in the urine is found by multiplying the predicted inulin clearance by the midpoint plasma inulin concentration, obtained as has been described, and divid-

ing this product by the urine flow in cubic centimeters per minutes, thus,

$$U = \frac{C_i B}{V}$$
 With these estimated urine and blood concentrations as guides, the protein-free filtrates are diluted to fall within the range of the method employed for analysis of inulin. Occasionally it may be necessary to repeat the dilutions when one has assumed a clearance which happens to lie very far above or below the patient's true functional level.

For analysis of inulin, the colorimetric method of Alving, Rubin and Miller²⁰ is employed. This method is simple enough to be performed with ease in any well equipped clinical laboratory. The analytic technique is the same for serum, plasma or urine. The procedure is given in brief outline here in order to give the reader some idea of the apparatus and time required for the analyses. Those who wish to employ the method should refer to the original papers, which describe the technical details.

Dextrose is removed from plasma, serum or urine by fermentation. Filtrates are prepared from the fermented samples and are diluted, if necessary, to contain between 0.002 and 0.012 mg. of inulin per cubic centimeter. Five cubic centimeters of each filtrate is placed in a special pressure-resistant glass tube and mixed with 10 cc. of freshly prepared acid-alcohol-diphenylamine reagent. The tube is heated in a vigorously boiling water bath for one hour. Up to thirty-six tubes may be carried through the analysis at one time. The tubes are cooled to room temperature by immersion in cold water. The clear blue color given by the inulin is quantitated in an Evelyn photoelectric colorimeter or a visual colorimeter. Blank analyses performed on reagents and distilled water correct for any color added by these solutions.

Calculation of the Plasma Concentration When a Sample of Blood Cannot Be Obtained at the Exact Midpoint of the Clearance Period—If the sample of blood is not obtained at the exact midpoint, the correct value may be calculated as follows. On semilogarithm graph paper the two concentrations of blood inulin are plotted on the logarithmic coordinate against time on the linear coordinate. A straight line is drawn between the two blood concentrations. The plasma concentration corresponding to the midpoint of the clearance period is then obtained, and this value may be taken as the mean plasma concentration for the period. For ordinary clinical purposes this correction should be applied only when a sample of blood is obtained two or more minutes from the midpoint.¹⁷

Calculation of the Inulin Clearance (or Glomerular Filtration Rate)—The plasma (or serum) inulin clearance is calculated from the formula $C_i = U V/B$, in which

C_i = cc. of plasma cleared of inulin per minute per 1.73 square meters of surface area (average human subject)

U = urine inulin concentration in milligrams per hundred cubic centimeters

B = mean plasma (or serum) inulin concentration in milligrams per hundred cubic centimeters

V = urine volume in cubic centimeters per minute

The clearance when obtained for adults of average size by this calculation does not need further correction. However, when clearance tests are performed on children or on adults who deviate from the norm or when highest precision is desired, the urine volume should be corrected for the subject's deviation from average surface area. The proper correction factors are given by Peters and Van Slyke²¹

The absolute inulin clearance obtained by the foregoing calculations is divided by 1.25 whenever it is desirable to express the inulin clearance (or glomerular filtration rate) in percentage of average normal

COMMENT

The test for inulin clearance, or glomerular filtration rate, described here is a simple enough procedure to be done in almost any hospital. The test demands little from the patient and can be performed safely on very ill persons. The analytic skill required for the analyses of inulin is about the same as for any of the blood chemistry determinations in current use. Because of the simplicity of the test and the attractiveness of the idea of obtaining a well defined measurement of function of the kidney in disease there may be a tendency to exaggerate the applicability of this test. It seems to us that the inulin clearance test has an important application in clinical studies of patients in whom renal function is deranged. On the other hand, there seems little point in supplanting the entirely satisfactory urea clearance, fractional phenol-sulfonphthalein or urine concentration tests for routine diagnosis and follow-up of patients.

Estimation of the glomerular filtration rate by the inulin clearance enables one to make a number of calculations of the excretion characteristics of the kidney in disease. For example, the glomerular filtration rate minus the rate of urine flow gives the amount (in cubic centimeters) of water reabsorbed per minute by the tubules. Such a measurement has obvious applications in the study of water excretion under the influence of various diuretics or in such a disease as diabetes insipidus.

Furthermore, whenever another substance is as freely filtrable from the plasma as inulin²² its clearance value in relation to the inulin clearance permits important deductions. If the clearance of a compound is

21 Peters, J. P., and Van Slyke, D. D. *Quantitative Clinical Chemistry*, Baltimore, Williams & Wilkins Company, 1932, vol. 2, p. 568.

22 The "filtrability" of a substance is usually determined by measuring its diffusibility through membranes of known pore size by means of an ultrafiltration apparatus such as has been described by P. H. Laviertes (*Anaerobic Ultrafiltration*, *J. Biol. Chem.* **120**: 267 [Aug.] 1937).

lower than that of inulin, the compound has been reabsorbed in the tubules. The extent of reabsorption is calculated very simply as (inulin clearance—clearance of "X")/inulin clearance. For example, with an adequate urine flow, the mean plasma urea clearance for a normal man of average size is 70 cc per minute^{5a}. It is known that urea is filtered from the plasma as readily as inulin. Therefore, the reabsorption of urea is calculated as $\frac{125-70}{125} \times 100$, which equals 44 per cent. Now consider an example which illustrates the striking changes that may be observed in disease when simultaneous urea and inulin clearances are performed. McCance and Widdowson²³ made such a comparison in cases of diabetic acidosis and observed a complete derangement of this normal relation. Calculation of the tubular reabsorption of urea from the data on one of these subjects follows. In this patient the inulin clearance was 31.8 cc per minute and the urea clearance 3.6 cc per minute. Therefore the per cent reabsorption was $100 \times \frac{11.8-3.6}{31.8}$, or 89 per cent of the filtered urea. This striking derangement of the normal activity of the tubular system with respect to urea could have been demonstrated convincingly only by comparing the urea clearance with the filtration rate. McCance and Widdowson further demonstrated that the tubules in a patient with diabetic acidosis may be abnormal with respect to the excretion of exogenous creatinine and the reabsorption of sodium, chloride and dextrose.

Important calculations may be made on the excretion characteristics of dextrose. Normally the clearance of dextrose is zero, indicating complete tubular reabsorption of this compound. In diabetes, the clearance becomes positive as glycosuria develops. The actual quantity of dextrose reabsorbed per minute may be calculated as follows (the inulin clearance minus the dextrose clearance) multiplied by the concentration of dextrose in the blood plasma is equal to the amount of sugar reabsorbed. As was shown by Shannon and Fisher,^{5b} this value for the normal kidney approaches a well defined limit which equals the maximal reabsorptive capacity of the tubular system with respect to dextrose. A maximal reabsorptive capacity has been demonstrated also for ascorbic acid²⁴.

Recently, Coombs and Talbott,²⁵ by comparing the clearance of uric acid with the inulin clearance, studied the ability of gouty patients to excrete uric acid.

23 McCance, R. A., and Widdowson, E. M. Functional Disorganization of the Kidney in Disease, *J. Physiol.* **95** 36 (Jan.) 1939.

24 Ralli, E. P., Friedman, G. J., and Rubin, S. H. The Mechanism of the Excretion of Vitamin C by the Human Kidney, *J. Clin. Investigation* **17** 765 (Nov.) 1938.

25 Coombs, F. S., and Talbott, J. H. The Mechanism of Uric Acid Elimination by the Kidney, *J. Clin. Investigation* **18** 490 (July) 1939.

When a substance has a clearance higher than that of inulin, it is excreted presumably partly or completely by the renal tubules. Exogenous creatinine is such a substance, and comparison of its clearance with that of inulin^{6c} demonstrated its true mode of excretion by the human kidney and proved the error involved in Rehbeig's assumption that the clearance of exogenous creatinine may be employed for clinical study of the filtration rate. When the excretion of endogenous creatinine was studied in man⁹ it appeared that this compound was excreted in part by the tubules in cases of advanced renal damage, whereas in the normal kidney such tubular secretion was not constantly present. Phenolsulfonphthalein, diodrast and hippuran are other substances which are excreted largely by the tubules, as is shown by comparison of their clearances with the inulin clearance.^{7d}

It is hoped that application of the inulin clearance measurement in various clinical conditions will give a better understanding of the deranged renal function associated with them. For example, the reason for the elevated level of blood urea associated with Addison's disease has not been elucidated completely. Also, the role of the kidney in the so-called extrarenal azotemias has not been studied extensively by modern techniques. Many of these interesting derangements of the renal excretory mechanism occur in diseases which lie outside the province of investigators of "renal disease." It is possible with the method outlined in this paper to obtain precise information of certain excretion characteristics of the kidney in all diseases in which derangement of renal function is suspected. By doing so, it should be possible in the future to give precise estimates of the changes which have occurred in specific functions and anatomic sections of the nephron and thereby avoid descriptions of the pathologic physiology of the kidney in such vague terms as "impairment of kidney function."

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PURPURA HAEMORRHAGICA DUE TO THE ARSPHENAMINES

SENSITIVITY IN PATIENTS AS INFLUENCED BY
VITAMIN C THERAPY

ERNEST H FALCONER, M D

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AND

EDITH S MILLS, M A

SAN FRANCISCO

Since 1933 we have had an opportunity to study 7 patients showing reactions accompanied by thrombopenic purpura following arsphenamine therapy. These patients have submitted to further injections of arsphenamine preparations, thereby we have been allowed to reproduce experimentally their attacks of purpura. An opportunity has thus been afforded for study of the effects of oral and parenteral administration of vitamin C on this type of sensitivity.

Our interest in the effect of vitamin C on purpura due to administration of neoarsphenamine was stimulated by reports in the literature that tended to show a relationship between vitamin C deficiency and arsphenamine sensitivity and also by reports of the clinical use of vitamin C as an agent to ameliorate the toxic effects of the arsphenamines. We have been interested also in several reports concerning the therapeutic value of ascorbic acid in the treatment of patients having idiopathic thrombopenic purpura.

In 1935 Sulzberger and Oser¹ published results, obtained from experiments on guinea pigs, which tended to show that animals on a diet deficient in vitamin C were more easily sensitized to neoarsphenamine by intracutaneous injection of the drug than were animals on a diet to which a daily dose of 2 mg of vitamin C had been added. Streitmann and Wiedmann² reported similar experiments in which

This study was aided by a grant from the Christine Breon Fund.

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1 Sulzberger, M. B., and Oser, B. L. Influence of Ascorbic Acid of Diet on Sensitization of Guinea Pigs to Neoarsphenamine, *Proc Soc Exper Biol & Med* **32** 716, 1935.

2 Streitmann, B., and Wiedmann, A. Biologische Pruefungen von Arsenobenzolderivaten. II. Vergleichende Untersuchungen ueber die Sensibilisierungsfahigkeit einzelner Arsenobenzolderivate, *Arch f Dermat u Syph* **175** 696, 1937.

guinea pigs receiving winter diets (dry fodder) plus vitamin C were less easily sensitized to neoarsphenamine than were those on the winter diets alone. Cormia³ reported experiments indicating that guinea pigs on diets low in vitamin C exhibited reactions to intracutaneous injections of neoarsphenamine of longer duration and of greater severity than the reactions of those on an adequate diet. In animals on a diet containing 50 Gm of ascorbic acid daily, he found that sensitization to arsphenamine was difficult to induce. Cormia⁴ reported 6 cases in which the onset of dermatitis followed the administration of arsphenamine and in which improvement of the eruption occurred after the administration of large doses of vitamin C. In 2 or 3 cases of dermatitis, the arsphenamine preparation that had previously caused reactions was tolerated without untoward results after large preliminary doses of vitamin C had been given intravenously.

Experimentation on animals with results exactly opposite to those already described were reported by Chapman and Morrell,⁵ who found that guinea pigs on a diet low in vitamin C became sensitive to arsphenamine less readily than the animals on a normal diet.

Recent carefully controlled studies by Cohen⁶ showed no difference in sensitivity to neoarsphenamine between guinea pigs on a diet low in vitamin C and those on what he termed "a tooth-protective ration." Cohen employed the microscopic appearance of developing teeth in the guinea pig as the criterion for insufficient vitamin C in the ration. He has stated that this is the most sensitive and reliable test for vitamin C deficiency in the guinea pig.

In connection with the results of investigators using vitamin C clinically to diminish the toxic reaction of the arsphenamines, the report of Friend and Marquis⁷ is of interest. These authors determined the vitamin C content of the blood of patients who had exhibited signs of sensitiveness to the form of arsphenamine they were receiving. The average reading for untreated patients was 0.64 mg per hundred cubic centimeters of blood. The average reading for patients receiving treat-

3 Cormia, F. E. Experimental Arsphenamine Dermatitis. The Influence of Vitamin C in the Production of Arsphenamine Sensitiveness, *Canad. M. A. J.* **36**: 392, 1937.

4 Cormia, F. E. Experimental Arsphenamine Sensitization. Further Observations on the Reactions to Arsphenamine in Guinea Pigs Given Staphylococcus Toxin, and in Guinea Pigs with Induced Streptococcal Infection, *J. Invest. Dermat.* **1**: 199, 1938.

5 Chapman, C. W., and Morrell, C. A. Influence of Vitamin C on Development of Skin Sensitivity to Neoarsphenamine in the Guinea Pig, *Proc. Soc. Exper. Biol. & Med.* **32**: 813, 1935.

6 Cohen, M. B. Vitamin C Deficiency. Sensitivity to Neoarsphenamine and Anaphylactic Shock, *J. Allergy* **10**: 15, 1938.

7 Friend, D. G., and Marquis, H. H. Arsphenamine Sensitivity and Vitamin C, *Am. J. Syph., Gonorr. & Ven. Dis.* **22**: 239, 1938.

ment with the arspnenamines was 0.63 mg per hundred cubic centimeters. The readings for 5 patients with arspnenamine reactions varied from 0.13 to 0.35 mg, with an average for the group of 0.25 mg per hundred cubic centimeters of blood. Their conclusion was that a low vitamin C content in the plasma was the result of the toxic reaction to the arspnenamines rather than a predisposing factor to such reactions.

Dainow⁸ stated that vitamin C increased a patient's tolerance to the arspnenamines, he stated further that his patients with low contents of vitamin C in their diet showed lack of tolerance to the arspnenamines. He concluded that vitamin C prevents the oxidation of arspnenamine in the tissues and thereby decreases its toxic action in the body.

Reports concerning the influence of vitamin C in controlling the hemorrhages in cases of idiopathic thrombopenic purpura indicate conflicting opinions as to its therapeutic effect. Boger and Schroder⁹ described a patient of their series, an elderly man with thrombopenic purpura who after four daily injections of 150 mg of ascorbic acid given intravenously ceased bleeding. After one month of further daily injections of 100 mg of ascorbic acid, the platelet count rose to 304,000 per cubic millimeter. Winckelmann¹⁰ treated 1 patient with idiopathic thrombopenic purpura by administering large doses of ascorbic acid, with apparently satisfactory results. This author attributed the reported failures as due to the use of too small doses of vitamin C. He advocated using a dose sufficient to saturate the tissues and the urine. He mentioned the use of doses as high as 1,000 to 1,500 mg of ascorbic acid daily.

Vogt¹¹ reported 2 cases of thrombopenic purpura, the diagnosis in 1 case being doubtful, in which daily treatment was given, with 2 to 6 cc of a solution of ascorbic acid (100 to 300 mg of ascorbic acid crystals), with good results. He believed that vitamin C strengthened the capillaries and prevented capillary leakage of blood. Miller and Rhoads¹² treated 4 patients with idiopathic thrombopenic purpura by administration of vitamin C. For 2 of the 4 patients the excretion of ascorbic acid was measured quantitatively to test the relative degree of saturation with vitamin C. In both patients clinical improvement

8 Dainow, I. Intolérance aux arsénobenzènes et vitamin C, *Presse med* **45** 1670, 1937.

9 Boger, A, and Schroder, H. Ueber die Stillung schwerster Blutungen bei allen Formen der hamorrhogischen Diathese und der Hemophilie durch parenterale Zufuhr von C-vitamin (Cebion Merck), *Munchen med Wchnschr* **81** 1335, 1934.

10 Winckelmann, H. Zur Vitamin C Behandlung von hamorrhagischen Diathesen, *Med Klin* **34** 906, 1938.

11 Vogt, E. Ueber die Behandlung gynakologischer Blutungen mit Vitamin C, *Munchen med Wchnschr* **82** 263, 1935.

12 Miller, D K, and Rhoads, C P. Ascorbic Acid in the Treatment of Thrombocytopenic Purpura, *J Clin Investigation* **15** 462, 1938.

and an increase in thrombocytes were associated with an increased urinary output of ascorbic acid. Boger and Morton¹³ reported that the administration of 200 mg daily of ascorbic acid to patients with thrombopenic purpura produced a marked rise in the number of platelets, with a decrease in bleeding.

Walther¹⁴ mentioned 3 patients with thrombopenic purpura who received from 100 to 500 mg of ascorbic acid daily, with no improvement that he could attribute directly to vitamin C.

Janet Vaughan¹⁵ reported a case of idiopathic thrombopenic purpura in which the patient was treated for five days with daily intravenous injections of 80 mg of ascorbic acid, with no improvement. Then from September 29 to November 2 the patient received 80 mg orally, which was increased to 160 mg daily from November 2 to December 13, with no improvement. Davidson¹⁶ treated 3 patients with thrombopenic purpura by intravenous injections of vitamin C, without improvement. Wright and Lilienfeld¹⁷ made a thorough study of the therapeutic possibilities of vitamin C (ascorbic acid). Their series included 3 patients with thrombopenic purpura. One of these patients, a woman aged 45, with a history of bleeding from the gums and nasal mucosa, was under observation for forty-five days. For seven days before admission to the hospital she received orally 90 mg of ascorbic acid daily. During the next thirty-eight days she received 100 mg daily, intravenously, except for two days when none was given and one day when 200 mg was administered. The patient appeared to be improving up to the thirtieth day, at which time she had a relapse while she was receiving a daily intravenous dose of 100 mg of ascorbic acid. The other 2 patients were children who received a daily intravenous injection of 100 mg of ascorbic acid, 1 for three weeks and the other for fourteen days. No definite improvement was evident in either patient.

METHOD

Six patients known to be sensitive to neoarsphenamine and 1 patient sensitive only to bismarsen were selected for this experimental study. These patients having been tested previously with varying doses of the arsphenamines, we had definite data concerning their sensitivity, and we believed the degree of sensitivity could be roughly estimated in each case. The previous reactions exhibited by these

13 Boger, A, and Morton, W. Vitamin C und Blut, *Munchen med Wchnschr* **82** 899, 1935.

14 Walther, G. Misserfolge bei Vitamin C Therapie, *Med Klin* **34** 260, 1938.

15 Vaughan, J. M. Treatment of Thrombocytopenic Purpura, *Brit M J* **2** 842, 1937.

16 Davidson, L. S. P., Davenport, C., and Rabagliati, D. S. Discussion on Purpuric Conditions in Man and Animals, *Proc Roy Soc Med* **30** 715, 1937.

17 Wright, I. S., and Lilienfeld, A. Pharmacologic and Therapeutic Properties of Crystalline Vitamin C (Cevitamic Acid) with Especial Reference to Its Effect on Capillary Fragility, *Arch Int Med* **57** 241 (Feb) 1936.

patients following the administration of neoarsphenamine or bismarsen consisted of toxic reactions varying from almost no symptoms in 1 case to marked prostration, nausea, vomiting, rapid pulse, chills and malaise and was followed in each instance by thrombopenic purpura. Up to this time no vitamin C had been administered to any of these patients before their reactions. In 1 case, following purpura and other hemorrhagic phenomena, vitamin C was administered. The diet of each patient was inquired into carefully, and for only 1 patient was the intake of vitamin C deemed inadequate.

The blood counts were done with pipets standardized by the United States Bureau of Standards. Hemoglobin estimations were made with the Sahli instrument, as modified by Osgood and Haskins¹⁸. With this instrument 13.8 Gm per hundred cubic centimeters of blood is considered normal. Platelet counts were made by the method of Rees and Ecker¹⁹. The capillary fragility tests were made with the Dalldorf²⁰ instrument. In each instance the reading was made after one minute of negative pressure. The amounts taken and the intervals during which these patients took vitamin C orally and intravenously varied considerably, but these amounts and the time intervals are recorded in the case reports which follow.

REPORT OF CASES

CASE 1—G. S., a woman aged 52, was being treated in the syphilitic clinic in 1933 and 1934, at which time she showed an initial sensitivity to neoarsphenamine after her first intravenous injection of 0.3 Gm. After the second injection of 0.15 Gm of the drug one week later, she had a toxic reaction followed by purpura haemorrhagica. Her case was reported in 1936²¹ as G. N., case 2.

On May 29, 1934, through an oversight on the part of the physician in charge of her treatment, she was given an intravenous injection of 0.3 Gm of neoarsphenamine. An immediate toxic reaction followed, with nausea, vomiting, chills and general malaise, and within twenty-four hours purpuric areas appeared in the buccal mucous membranes. On June 4, one week later, she received another injection of neoarsphenamine (0.3 Gm), which was followed immediately by a toxic reaction and after twenty-four hours by a generalized purpuric eruption. We have no record of her platelet count before these two intravenous injections of neoarsphenamine, but when she reported to the hematologic clinic on June 6, the platelet count was 10,000 per cubic millimeter, and the bleeding time (Duke) was sixteen minutes.

On Feb. 8, 1935, approximately nine months later, an intravenous injection of 0.1 Gm of neoarsphenamine was administered in order to ascertain the state of the patient's sensitivity. Immediately after the injection her face became flushed, and she had nausea, vomiting and severe pains in the lumbar region. About thirty minutes after the injection a chill supervened, and at the one hour period

18 Osgood, E. E., and Haskins, H. D. A New Permanent Standard for Estimation of Hemoglobin by the Acid Hematin Method, *J. Biol. Chem.* **57**:107, 1923.

19 Rees, H. M., and Ecker, E. E. An Improved Method for Counting Blood Platelets, *J. A. M. A.* **80**: 621 (March 3) 1923.

20 Dalldorf, G. A Sensitive Test for Subclinical Scurvy in Man, *Am. J. Dis. Child.* **46**: 794 (Oct.) 1933.

21 Falconer, E. H., Epstein, N. N., and Wever, G. K. Purpura Haemorrhagica Following the Administration of Neoarsphenamine. Reaction to Neoarsphenamine Compared with Reaction to Mapharsen, *Arch. Int. Med.* **58**: 495 (Sept.) 1936.

the platelet count had fallen from 300,000 before the injection to 20,000. At this time there was bleeding from the nasal mucosa, and purpuric lesions were appearing over the lower extremities with a few hemorrhagic blebs in the buccal mucous membranes. On March 8, about nine days after the injection, the platelet count had increased to 230,000 and the purpuric lesions had nearly disappeared.

After three years, during which time the patient had been free of symptoms and had received no treatment with arsenicals, she returned on March 12, 1938, for further tests to determine the status of her sensitivity to neoarsphenamine. We planned to study the effects of vitamin C therapy on this sensitivity, par-

TABLE 1—*Data in Case 1*

Date	Time	Platelet Count*	White Cell Count
3/12/38	Before administration of neoarsphenamine	250,000	8,200
	15 minutes after	110,000	6,800
	30 minutes after	120,000	7,100
	60 minutes after	120,000	8,400
	2 hours after	80,000	9,300
3/14/38	2 days after	180,000	8,350
3/16/38	4 days after	210,000	6,750
3/21/38	Before administration of neoarsphenamine	260,000	7,950
	15 minutes after	150,000	4,900
	30 minutes after	110,000	5,100
	60 minutes after	150,000	5,900
	2 hours after	160,000	6,100
	2½ hours after	30,000	6,050
3/22/38	24 hours after	110,000	8,500
3/25/38	4 days after	270,000	8,400
5/24/38	Before administration of neoarsphenamine	390,000	5,800
5/31/38	Before administration of neoarsphenamine	290,000	6,500
	15 minutes after	100,000	1,900
	30 minutes after	95,000	7,700
	60 minutes after	60,000	4,800
	2 hours after	90,000	3,900
	5 hours after	110,000	6,000
	7 hours after	120,000	6,250
6/ 1/38	26 hours after	20,000	7,800
6/ 2/38	2 days after	110,000	5,400
6/ 3/38	3 days after	150,000	8,200
6/ 4/38	4 days after	220,000	6,300
6/ 7/38	7 days after	360,000	8,900

* The platelet counts from March 12 to 16 inclusive were made after the administration of 0.01 Gm of neoarsphenamine, before therapy with ascorbic acid; the counts from March 21 to 25 inclusive were made after the administration of 0.015 Gm of neoarsphenamine, before therapy with ascorbic acid; the counts from May 31 to June 7 inclusive were made after the administration of 0.0075 Gm of neoarsphenamine, after nine weeks' therapy with ascorbic acid.

ticularly with respect to its influence on the toxic reaction and purpuric phenomena which invariably followed the administration of neoarsphenamine. On the day of her return the patient was given an intravenous injection of 0.01 Gm of neoarsphenamine, an amount one-tenth the size of the dose that had caused a sharp reaction three years before. Immediately after this injection she had a constitutional reaction and purpuric phenomena of the same type as those already described as following the administration of 0.1 Gm of neoarsphenamine on Feb 8, 1935, with the exception that the symptoms were milder, the purpuric eruption being confined to the lower extremities and the lesions consisting of fine, scattered petechiae, which could be well made out with the aid of a hand lens. The effect on the platelet level is shown in table 1.

Nine days later, on March 21, we administered a second injection of neoarsphenamine, increasing the dose slightly to 0.015 Gm. An immediate toxic reaction occurred, followed by the appearance of purpuric lesions over the upper and lower extremities two and one-half hours after the injection. At that time the

platelet count showed a drop from 260,000 before the injection to 30,000. All the sensitivity phenomena were intensified with this slightly larger dose of neoarsphenamine. We felt that if we now gave the patient sufficient vitamin C therapy to saturate the tissues, and if we repeated the dose of 0.01 Gm of neoarsphenamine, which had produced a mild reaction, we could readily assess the value of vitamin C as a protective agent capable of diminishing the toxic symptoms of neoarsphenamine and of preventing the development of purpura through inhibiting capillary fragility. At this time, as the next step in the experiment, the patient was given a list of the natural sources of vitamin C and was instructed concerning a diet with an abundance of this vitamin, from two to three glasses of orange juice daily being included. After one month of this regimen, 1 tablet of ascorbic acid, containing 0.25 mg, three times per day was added, to be taken by mouth along with the diet. After three weeks of this diet, plus 75 mg of ascorbic acid taken orally each day, additional vitamin C in the form of 100 mg of ascorbic acid was injected intravenously every third day for fifteen days. At the end of nine weeks of increasing the vitamin C intake, we felt that the tissues were well saturated with vitamin C, a condition which, should it prove efficient in diminishing sensitivity to neoarsphenamine, would allow the patient to receive a dose of 0.01 Gm of the drug with a minimum of reaction and slight, if any, purpuric or hemorrhagic phenomena. It will be recalled that on March 12, after the administration of 0.01 Gm of neoarsphenamine, the patient had a relatively mild toxic reaction, with scattered, fine petechiae over the lower extremities. We were entirely unprepared for the startling reaction that followed our attempt to give 0.01 Gm of neoarsphenamine on May 31. At 8 a. m. the platelet count was 290,000. At this time 100 mg of ascorbic acid was administered intravenously. One hour later 100 mg was given subcutaneously and was followed by the intravenous injection of neoarsphenamine. As soon as the solution began to flow into the vein, the patient became flushed over the face and neck. She complained of a smothering sensation, the pulse became rapid and feeble, as collapse was imminent, the needle was withdrawn after 0.0075 Gm of the drug had been administered. The blood pressure, which had been 130 systolic and 80 diastolic before the injection, fell rapidly to 80 systolic and 60 diastolic, and as the needle was withdrawn the patient passed quickly into a state of profound shock. The radial pulse could not be felt, and the extremities were cold and cyanotic. Restorative measures were administered in succession, beginning with application of heat to the body and followed by two subcutaneous injections of 1 cc each of epinephrine (1:1,000) and intramuscular injection of 0.5 cc of caffeine with sodium benzoate. After one hour, 1 liter of 5 per cent dextrose solution, to which was added 1 cc of epinephrine (1:1,000), was administered intravenously. The platelet count dropped to 100,000 fifteen minutes after the drug had been administered, at one hour the count was 60,000, and purpuric lesions were appearing over the neck, the upper part of the chest, the arms and the lower extremities (table 1, fig 1). After eight hours the patient felt recovered from shock and insisted on being taken home. On the following morning we called at her home, feeling much concerned about her condition. As we entered her room, the sight presented was astonishing. On the floor were several heaps of towels and cloths soaked with blood. The bed sheets and pillow covers were saturated with large blood stains. Wrapped about the patient's head was a large bath towel saturated with blood. All this bleeding came from the tiny needle punctures in the lobe of the ear, the punctures having been made the previous day at the laboratory. As these punctures were still oozing, the patient was sent by ambulance to the hospital where pressure and thromboplastin applied locally

checked the bleeding. She recovered rapidly in three days without any special treatment and was discharged from the hospital. The platelet count at entry was 20,000, at discharge, 150,000, and at the end of one week after administration of the drug, 360,000 (table 1). The red cell count dropped in four days after injection from 5,300,000 to 3,710,000. The hemoglobin value dropped from 12.88 Gm (94 per cent) to 10.49 Gm (78 per cent).

Comment—The results of the experiment on this patient were so striking and dramatic that comment seems scarcely necessary. However, some features deserve brief mention, particularly her sensitivity to neoarsphenamine. This sensitivity appeared to be little changed in the three year period since Feb. 18, 1935, when she was given 0.1 Gm of neoarsphenamine, the administration of which was followed by a



Fig. 1 (case 1)—Photograph showing ecchymoses following administration of 0.0075 Gm of neoarsphenamine, after nine weeks of preliminary therapy with vitamin C.

toxic reaction and a purpuric eruption. The injections of neoarsphenamine on March 12 and 21, 1938 appeared to increase her sensitivity markedly, and the subsequent nine weeks of abundant intake of vitamin C, in both the natural and the crystalline forms, did not reduce this sensitivity, compared with her previous reactions. In fact, it would appear as if the vitamin C intake actually enhanced her sensitivity to neoarsphenamine. This conclusion, however, is not warranted without an adequate control experiment, which was obviously not possible in this type of experiment.

The pronounced hemorrhagic features of her last reaction, May 24, 1938, as evidenced by the drop in the hemoglobin value and the red cell count over a period of four days, were far in excess of those observed at the six previous reactions studied by us, although with two of these

reactions the platelet count fell to lower levels than on May 24. On June 4, 1934, after the administration of 0.3 Gm of neoarsphenamine, the platelet count dropped at the end of the second day to 10,000, on Feb 28, 1935, one hour after the administration of 0.1 Gm of neoarsphenamine, the platelet count dropped to 20,000, and two days later it dropped to 10,000.

To one interested in the study of purpura haemorrhagica, this is an important observation, suggesting as it does that the platelet level in itself is not the determining factor causing hemorrhage, but that rather loss of tone in the capillary bed is the direct factor influencing the degree of bleeding that takes place from the capillaries.

TABLE 2—Data in Case 2

Date	Time	Platelet Count*	White Cell Count
1/21/37	Before administration of neoarsphenamine	290,000	6,200
	15 minutes after	50,000	
	30 minutes after	30,000	
	45 minutes after	30,000	
	60 minutes after	20,000	
	5 hours after	20,000	7,100
1/22/37	30 hours after	30,000	7,450
1/26/37	5 days after	50,000	7,300
1/28/37	7 days after	150,000	7,500
2/ 3/37	13 days after	450,000	9,450
1/12/38	Before administration of neoarsphenamine	310,000	8,000
	15 minutes after	90,000	3,400
	30 minutes after	70,000	3,500
	45 minutes after	90,000	9,800
	60 minutes after	90,000	9,700
	8 hours after	120,000	11,500
1/13/38	24 hours after	25,000	5,400
	30 hours after	60,000	5,500
1/14/38	2 days after	80,000	7,300
1/20/38	8 days after	310,000	7,400
1/22/38	10 days after	390,000	7,900

* The platelet counts from Jan 21 to Feb 3, 1937 inclusive were made after the administration of 0.0075 Gm of neoarsphenamine, before therapy with ascorbic acid, the counts from Jan 12 to 22, 1938 inclusive were made after the administration of 0.0001 Gm of neoarsphenamine, after eight weeks' therapy with ascorbic acid.

CASE 2—E G, a woman aged 44, had previous reactions which had shown her to be very sensitive to neoarsphenamine. On Jan 21, 1937 we gave her an intravenous injection of 0.0075 Gm of neoarsphenamine to determine the degree and intensity of her reaction to this small amount of the drug. While she was receiving the injection her face and neck became flushed, then cyanotic. She felt a sense of suffocation. After the needle was withdrawn, nausea and vomiting occurred, the hands and feet became cold and the pulse rapid. Fifteen minutes after the injection the platelet count had dropped from 290,000 before injection to 50,000 (table 2), and at the end of thirty minutes the number of platelets had fallen to 30,000 per cubic millimeter. The reaction was marked, but the acute symptoms subsided in about two hours. On the following day the neck, the shoulders, the anterior portion of the chest and the extremities were covered with a petechial eruption. The oral mucous membranes showed a few hemorrhagic blebs, there was a small amount of uterine bleeding, and the urine showed many red blood cells.

Five days after this injection of neoarsphenamine the platelet count was 50,000, on the thirteenth day it was 450,000 (table 2).

On November 15 the patient was placed on a diet containing an abundance of fresh vegetables and, in addition, two glasses of orange juice daily. After twenty-five days 4 tablets daily by mouth were added to the diet, each tablet containing 25 mg of ascorbic acid (500 international units). On Jan 3, 1938, twenty-one days after administration of the tablets was begun, intravenous injection of an additional 100 mg of ascorbic acid was instituted. She received five such doses at two day intervals.

With this preparation of approximately eight weeks of vitamin C therapy, the patient received on January 17 an intravenous dose of 0.0001 Gm of neoarsphenamine. This amount was dissolved in 10 cc of distilled water and injected slowly. Before she had received half the dose, her face and neck became flushed, she felt "as if she were choking," and the pulse became extremely rapid. At the



Fig 2 (case 2) —Photograph showing large ecchymotic areas the development of which followed administration of 0.0001 Gm of neoarsphenamine, after preliminary therapy with vitamin C

end of the injection, prostration was marked, she had a severe headache and vomited. Fifteen minutes after the injection the platelet count had fallen from 310,000 before injection to 90,000, at the end of thirty minutes the count was 70,000. Eight hours after the injection of neoarsphenamine the patient was sufficiently recovered to eat a light repast with a cup of coffee, after which the platelet count rose slightly (table 2). On the following day the platelet count was 25,000. A fine petechial eruption covered the upper part of the chest, the shoulders and the upper and lower extremities. Over both calf regions were ecchymotic areas about 3 by 4 cm. Forty-eight hours after the injection the platelet count was 80,000, the patient complained of feeling very weak, with generalized pain over the body. Eight days after the injection there were large ecchymotic areas over the calf muscles of both legs (fig 2).

Comment—This patient was known to be very sensitive to neoarsphenamine, but we believed the dose administered after preliminary vitamin therapy was so small as to preclude anything but a mild reaction. We felt that the preliminary vitamin C therapy might eliminate the toxic reaction and purpuric manifestations entirely. The rapid and severe reaction that followed this small dose of neoarsphenamine surprised us greatly and left us with the definite impression that vitamin C therapy had no effect in diminishing sensitivity to neoarsphenamine in this patient nor in ameliorating the toxic effects of the drug.

It should be noted that the time interval between the two doses of neoarsphenamine described in this experiment was approximately one year and that no neoarsphenamine had been administered between the doses mentioned, there was no chance for sensitization to become enhanced during the interval by reason of administration of any of the arsenicals, with the exception of mapharsen, to which the patient never showed evidences of sensitization.

CASE 3—A LaG, an obese woman aged 48, showed a marked reaction to bismarsen accompanied by thrombopenia and purpura, but she showed no reaction and no purpuric manifestations after administration of neoarsphenamine. When 0.1 Gm of sulfarsphenamine was given intravenously, this patient went into a state of profound shock, pulmonary edema rapidly supervened, and after twenty-four hours mild bronchopneumonia occurred, from which she made a satisfactory recovery after eleven days in the hospital.

On Dec 30, 1938 she was given a dose of 0.1 Gm of bismarsen intramuscularly. This occurred before she had received 0.1 Gm of sulfarsphenamine intravenously, and is recounted here to indicate her reaction to bismarsen for later comparison. The platelet count before this injection was 570,000 at one and one-half hours, after the injection it was 210,000. Immediately after receiving the drug she became pale and nauseated, the pulse was rapid and feeble, and the extremities were cold. At one and one-half hours, a chill occurred which necessitated a subcutaneous injection of 1 cc of epinephrine (1:1,000). The platelet count rose after the injection of epinephrine, and in one-half hour the count was 320,000 per cubic millimeter. On the following day the platelet count was 60,000, and there was a marked purpuric eruption over the shoulders, the anterior part of the chest, the abdomen and the upper and lower extremities. On the sixth day after the injection the platelet count was 320,000, and the patient had recovered from her toxic reaction. About six months after the reaction just described (June 22, 1939), the patient reported for further studies of the effect of vitamin C therapy on sensitivity. Before therapy was started, she had a vitamin C level in the plasma of 0.63 mg per hundred cubic centimeters of blood. She received 100 mg of ascorbic acid intravenously, and on the following day she began to take 4 tablets daily of ascorbic acid by mouth, each tablet containing 25 mg. The tablets were given daily from June 22 to July 12, the intravenous injection of vitamin C, the administration of 100 mg of ascorbic acid, was performed every second day during this period, in addition to including in her diet two oranges daily. The level of vitamin C in her blood plasma during this period is recorded in table 3. On July 10 the vitamin C in the plasma was 1.20 mg per hundred cubic centimeter of blood. On July 12 it was 1.01 mg. On this date she received 100 mg of ascorbic acid intravenously at 9 a m, at 9:30 a m, 0.075 Gm of

bismarsen was injected in the left buttock At 9 45 the face was flushed, and the "gums throbbed" A slight suffocating sensation was felt at 10 a m Thirty minutes after the injection there was severe "backache," and at 10 15 a m vomiting and marked prostration At 10 50 a m a chill came on, and the vomiting continued for five hours after the injection of bismarsen Six hours after the injection, epistaxis appeared and also slight uterine bleeding, although her menstrual flow had ceased on June 26 About ten hours after the injection of bismarsen bleeding occurred from the needle puncture in the lobe of the left ear On the following day, July 13, a purpuric eruption was present over the neck, the shoulders, the anterior

TABLE 3—Data in Case 3

Date	Time	Platelet Count*	White Cell Count	Plasma Vitamin O Content, Mg per 100 Cc of Blood
12/30/38	Before administration of bismarsen	570,000	9,200	
	15 minutes after	510,000	7,800	
	30 minutes after	460,000	16,000	
	60 minutes after	300,000	12,100	
	1½ hours after	210,000	9,300	
	2 hours after	320,000	9,100	
	3 hours after	170,000	8,400	
12/31/38	24 hours after	60,000	11,500	
	34 hours after	80,000	12,100	
1/ 3/39	4 days after	110,000	15,750	
1/ 4/39	5 days after	160,000	19,100	
1/ 5/39	6 days after	320,000	17,300	
6/22/39	Before administration of bismarsen	360,000	11,300	0.63
6/24/39	Before administration of bismarsen	310,000	16,100	
6/26/39	Before administration of bismarsen	400,000	12,600	0.75
6/28/39	Before administration of bismarsen	360,000	11,900	0.87
6/30/39	Before administration of bismarsen	370,000	10,700	0.93
7/ 5/39	Before administration of bismarsen	320,000	10,600	0.57
7/ 8/39	Before administration of bismarsen	360,000	10,800	1.07
7/10/39	Before administration of bismarsen	340,000	11,400	1.20
7/12/39	Before administration of bismarsen	350,000	12,500	1.01
	15 minutes after	240,000	5,850	
	30 minutes after	80,000	6,100	
	60 minutes after	60,000	8,400	
	2 hours	40,000	8,800	
	5½ hours after	50,000	10,900	
7/13/39	24 hours after	60,000	9,100	0.66
7/14/39	2 days after	70,000	8,800	0.82
7/15/39	3 days after	80,000	9,800	
7/17/39	5 days after	230,000	12,400	0.69
7/21/39	9 days after	340,000	7,800	

* The platelet counts from Dec 30, 1938 to Jan 5, 1939 inclusive were made after the administration of 0.1 Gm of bismarsen, before therapy with ascorbic acid the counts from July 12 to 21 inclusive were made after the administration of 0.075 Gm of bismarsen, after therapy with ascorbic acid

part of the chest and the upper and lower extremities In the subcutaneous tissues of the lower extremities there were a few ecchymotic areas, the largest being 3 by 5 cm in size In the mucous membranes of the soft palate a hemorrhagic bleb was present, 0.5 cm in diameter Nasal bleeding continued through July 14 On this date the purpuric lesions were large and distinct, several over the shoulders and the upper part of the chest were 0.5 cm in diameter This type of large, round, almost pure black purpuric lesion has been noted by us previously, particularly in connection with bismarsen sensitivity (fig 3) The platelet counts dropped rapidly after the injection, at the end of thirty minutes the count had fallen from 350,000 before the dose of bismarsen to 80,000 and at the one hour period still further, to 40,000 per cubic millimeter The platelet count was slow in rising (table 3) On July 15 the patient received 1 cc of Lederle's concentrated liver extract, and on July 17 the number of platelets had increased from 80,000 to 230,000

Comment—This was the only patient of the series sensitive to bismarsen and not to neoarsphenamine. She showed no sensitiveness to mapharsen. The experiment began about seven months after the last administration of bismarsen, but on Feb 20, 1939 she had experienced a severe reaction, with collapse and purpura haemorrhagica, from an intravenous injection of 0.1 Gm of sulfarsphenamine. The level of vitamin C in the plasma was up to normal (0.63 mg) at the beginning of therapy with ascorbic acid. On July 21, the date of the administration of 0.075 Gm of bismarsen, the vitamin C content of the plasma was 1.01 mg. The toxic reaction was more marked than her previous reaction to 0.1 Gm of bismarsen on Dec 30, 1938. The purpuric lesions are well shown in figure 2.

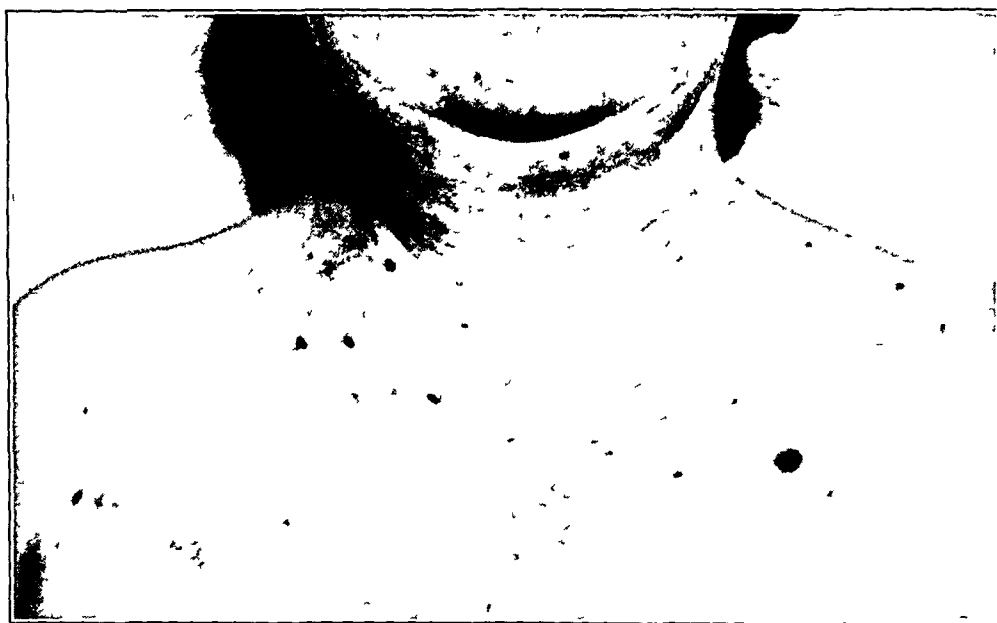


Fig 3 (case 3)—Large purpuric lesions the occurrence of which followed injection of 0.075 Gm of bismarsen, after therapy with ascorbic acid, the vitamin C content of the plasma being 1.20 mg per hundred cubic centimeters.

CASE 4—B. P., a Negress aged 30, was known to be sensitive to bismarsen and to neoarsphenamine. She became sensitive to bismarsen after fifty-three intramuscular injections. Just when she became sensitive to neoarsphenamine is not known, but the first reaction of which we have any record occurred on Oct 18, 1938, one month after discharge from the hospital where she had been under observation for five days on account of hemorrhage following the administration of bismarsen.

This reaction to neoarsphenamine, on October 8, followed the injection of 0.1 Gm of the drug, given intravenously. There were no subjective symptoms following administration, but there was a rapid drop in the platelet count from 380,000 before injection to 65,000 at the end of one hour, at which time purpuric lesions had appeared over the arms and lower extremities. At the end of four hours after injection the platelet count had dropped to 40,000. By the third day after the injection of neoarsphenamine, the number of platelets increased to 270,000 per cubic millimeter.

On June 26, 1939 we began further sensitivity studies on this patient. She gave the following interval history. While she was in the hospital during September 1938, it was learned that she was a morphine addict of long standing. After her discharge and up to the present, it had been increasingly difficult for her to obtain morphine. Recently she had been using an impure product of whole opium, injecting it beneath the skin. In addition to forming subcutaneous abscesses, this substance caused nausea, vomiting and anorexia, and for the past three or four months she had eaten chiefly carbohydrates, when she had been able to eat at all. As a result, the vitamin C content of her diet was considered to be entirely inadequate, an assumption supported by her low plasma content of vitamin C (table 4). While in the hospital in September 1938, she received 900 mg of ascorbic acid intravenously during forty-eight hours as a therapeutic measure for control of hemorrhage. The vitamin C content in the plasma at the end of that time was 0.42 mg per hundred cubic centimeters. We cannot judge as to the value of this therapy as we have no control observations.

On June 27 the vitamin C content in the plasma was 0.22 mg per hundred cubic centimeter of blood, on June 30 it was 0.17 mg. At 10 a. m. on this date she was given 0.1 Gm of neoarsphenamine, intravenously. Before administration of neoarsphenamine, the platelet count was 450,000, one-half hour after injection, 290,000, one hour after injection, 170,000, at two hours, 210,000, and after twenty-four hours, 260,000. There was no apparent toxic reaction after administration of the drug.

On July 6 the vitamin C content of the plasma was 0.25 mg per hundred cubic centimeters, the platelet count was 250,000. At this time 0.3 Gm of neoarsphenamine was administered intravenously. No toxic reaction occurred, but the blood pressure, which had been 120 systolic and 90 diastolic before administration of the drug, dropped to 85 systolic and 60 diastolic one-half hour after. The platelet count fell to 120,000 in fifteen minutes and to 100,000 at the end of one hour. As the patient had been without food all day and had a severe headache, she took a light repast with two cups of coffee about one and one-half hours after the injection. At the end of two hours the platelet count had risen to 120,000 per cubic millimeter. On the following day, twenty-four hours later, the platelet count was 20,000. There were a few small petechiae over the left lower extremity and over the upper anterior part of the chest on the left. The Dalldorf capillary fragility test showed at —15 cm pressure, a shower of petechiae, at —10 cm pressure, eight to ten petechiae. The platelet count returned to normal in five days.

On July 8 the vitamin C content in the plasma was 0.25 mg per hundred cubic centimeters, and oral administration of 1 tablet of ascorbic acid, 25 mg, was started four times daily. On July 11, 400 mg intravenously was added every second day up to July 19. The patient received 1,100 mg by mouth and 2,000 mg intravenously up to July 19, on which day 0.075 Gm of neoarsphenamine was given by vein. The vitamin C content of the plasma had increased to 1.01 mg by July 17, and to 1.5 mg by July 19. The blood pressure was 125 systolic and 90 diastolic before injection, and the platelet count was 350,000. Fifteen minutes after injection the platelet count was 120,000, at the end of thirty minutes the count was 50,000 platelets per cubic millimeter. The Dalldorf capillary fragility test at this time was at —15 cm pressure, 4 to 5 petechiae, at —10 cm pressure, none. Thirty minutes after the drug had been given the blood pressure was 80 systolic and 64 diastolic. At this time the patient felt weak and took a small amount of food, with a cup of coffee. One hour after injection the platelet count had risen to 105,000 per cubic millimeter. At the end of two hours the platelet

count was 50,000, and a small amount of bleeding from the nasal mucosa was present. During the evening of July 19 there was profuse uterine bleeding, nasal hemorrhage and bleeding from the gums. On the following morning there was much prostration, bleeding continued, the entire body was covered with a purpuric eruption, and several large ecchymotic areas were present. She was therefore admitted to the hospital. The platelet count at this time was 25,000, and the

TABLE 4—*Data in Case 4*

Date	Time	Platelet Count*	White Cell Count	Plasma Vitamin C Content, Mg per 100 Cc of Blood
10/18/38	Before administration of neoarsphenamine	380,000	9,800	
	15 minutes after	200,000	8,900	
	30 minutes after	110,000	8,500	
	60 minutes after	65,000	8,600	
	2 hours after	48,000	8,700	
10/19/38	4 hours after	40,000	8,800	
	24 hours after	100,000	9,100	
10/20/38	2 days after	270,000	8,900	
10/25/38	7 days after	340,000	9,000	
6/27/39	Before administration of neoarsphenamine	250,000	6,500	0.22
6/30/39	Before administration of neoarsphenamine	450,000	7,000	0.17
	15 minutes after	430,000	7,200	
	30 minutes after	290,000	8,100	
	60 minutes after	170,000	8,000	
	2 hours after	210,000	7,700	
7/ 1/39	24 hours after	260,000	9,100	0.17
7/ 6/39	Before administration of neoarsphenamine	250,000	11,200	0.25
	15 minutes after	120,000	9,700	
	30 minutes after	120,000	9,400	
	60 minutes after	100,000	9,500	
	2 hours after	120,000	10,100	
7/ 7/39	24 hours after	20,000	6,550	0.25
7/ 8/39	2 days after	70,000	6,750	0.25
7/11/39	5 days after	390,000	7,100	0.31
7/19/39	Before administration of neoarsphenamine	330,000	10,000	1.51
	15 minutes after	120,000	8,300	
	30 minutes after	50,000	12,200	
	60 minutes after	105,000	13,400	
	2 hours after	50,000	11,900	
	3 hours after	40,000	9,800	
7/20/39	24 hours after	25,000	9,900	1.13
	32 hours after	40,000	8,600	
7/21/39	48 hours after	40,000	10,400	1.20
	56 hours after	60,000	8,900	
7/22/39	3 days after	80,000	8,300	1.20
7/24/39	5 days after	480,000	7,400	0.88

* The platelet counts from Oct. 18 to 25, 1938 inclusive were made after the administration of 0.1 Gm. of neoarsphenamine, before therapy with ascorbic acid, the counts from June 30 to July 1, 1939 inclusive were made after the administration of 0.1 Gm. of neoarsphenamine, before therapy with ascorbic acid, the counts from July 6 to 11, 1939 inclusive were made after the administration of 0.3 Gm. of neoarsphenamine, before therapy with ascorbic acid, the counts from July 19 to 24, 1939 inclusive were made after the administration of 0.075 Gm. of neoarsphenamine, after therapy with ascorbic acid.

bleeding time was twenty-four minutes (Duke), with a nonretractile clot. Marked prostration was present. The blood pressure at 3 p. m. on July 20 registered 100 systolic and 66 diastolic. Just before neoarsphenamine was administered on July 19, 400 mg. of ascorbic acid was administered intramuscularly, this ended the therapy with ascorbic acid. On July 20 the vitamin C content in the plasma was 1.13 mg., a drop of 0.38 mg. in twenty-four hours. When one considers the fact that she had received 400 mg. intramuscularly on July 19, this appeared to be a significant fall. Also, the drop in the hemoglobin content and red blood cell content during the four days which followed the injection of neoarsphenamine

was striking. The red cell count fell from 4,560,000 to 4,010,000 and the hemoglobin content from 126 Gm (92 per cent) to 104 Gm (76 per cent). The patient was discharged from the hospital on July 22.

Comment—This experiment is the most interesting of the series, in that we were fortunate in securing a patient who was known to be sensitive to neoarsphenamine, whose vitamin C intake was inadequate and who showed a low vitamin C level in the blood (from 0.17 to 0.31 mg), figures which ordinarily cause one to suspect some clinical signs of vitamin C deficiency. In this connection it should be noted that the Dalldorf capillary fragility tests did not give the readings usually associated with vitamin C deficiency. This might be explained by the fact that the skin of both arms had been the site of trauma and irritation for many years, from self-administered hypodermics, thereby the capillaries were made unusually resistant. This patient has never exhibited any symptoms of a toxic reaction following administration of neoarsphenamine, hence the effects on the platelet count and the hemorrhagic manifestations are the factors to use in judging the degree of her sensitivity to the drug.

The intravenous injection of 0.1 Gm of neoarsphenamine, Oct 18, 1938, occurred exactly one month after the patient's discharge from the hospital where she had been treated for hemorrhagic phenomena (when she was given 0.2 Gm of bismarsen as part of her therapy for syphilis). During hospitalization she received 900 mg of ascorbic acid intravenously for treatment of the purpura. After one month, one would not expect this vitamin C to be still present in her system, nor did it appear to have influenced her sensitivity to neoarsphenamine, as the injection of 0.1 Gm of this drug on Oct 18, 1938 caused a marked diminution of the platelet count from 380,000 to 40,000 in four hours, with a purpuric eruption over the anterior part of the chest and the upper and lower extremities. Nine months later a similar dose of neoarsphenamine produced only a moderate drop in the platelet count (table 4), with no purpuric eruption, in the presence of a vitamin C level in the plasma of 0.17 mg per hundred cubic centimeters of blood. This is evidence that she had lost much of her sensitivity during the nine months since the previous injection of neoarsphenamine. The intravenous injection of 0.3 Gm of neoarsphenamine, six days later, produced a marked drop in the platelet count, from 250,000 to 20,000 in twenty-four hours, with a few purpuric lesions. This dose appeared to sensitize her to such an extent that, in spite of a high plasma vitamin C level of 1.51 mg she had a marked hemorrhagic reaction on being given 0.075 Gm of neoarsphenamine, a reaction more severe and prostrating than the reaction which sent her to the hospital after she was given 0.2 Gm of bismarsen on Sept 14, 1938.

CASE 5—M. M., a man of 66, was sensitive to neoarsphenamine and bismarsen. On Oct 21, 1937, he received 0.015 Gm of neoarsphenamine intravenously, with an immediate reaction characterized by cyanosis, rapid feeble pulse, nausea and pros-

tration He complained of feeling as if he was going to faint The drop in the platelet count is shown in table 5 At the end of thirty minutes after the injection the platelet count was 80,000, and at the end of two hours petechiae began to appear over the neck, the upper anterior part of the chest and the upper and lower extremities At this time he was seized by a chill for which a subcutaneous injection was given of 1 cc of epinephrine (1 1,000) The epinephrine caused a temporary rise in the platelet count (table 5) Prostration was so severe that we sent the patient into the hospital for observation over a twenty-four hour period Recovery was rapid, by October 25 the platelet count had returned to a level of 300,000 per cubic millimeter

On Jan 2, 1938 the patient began to take 3 tablets of ascorbic acid daily, each tablet containing 100 mg On January 6 he took only 1 tablet, but received 200 mg of ascorbic acid intravenously The second dose of 100 mg was administered five minutes before he received an intravenous injection of 0.005 Gm of

TABLE 5—Data in Case 5

Date	Time	Platelet Count*	White Cell Count
10/21/37	Before administration of neoarsphenamine	580,000	12,400
	15 minutes after	250,000	11,000
	30 minutes after	80,000	8,500
	60 minutes after	150,000	10,100
	2 hours after	170,000	13,900
	3 hours after	110,000	21,100
	7 hours after	190,000	14,800
10/22/37	24 hours after	100,000	12,600
10/23/37	2 days after	130,000	8,000
10/25/37	4 days after	300,000	11,200
10/26/37	5 days after	450,000	12,400
1/ 6/38	Before administration of neoarsphenamine	540,000	14,500
	15 minutes after	130,000	13,400
	45 minutes after	90,000	12,000
	60 minutes after	115,000	11,300
	1½ hours after	80,000	12,300
	5 hours after	55,000	36,000
1/ 7/38	24 hours after	190,000	17,400
	30 hours after	210,000	14,900
1/ 8/38	2 days after	320,000	14,100
1/13/38	7 days after	380,000	13,800

* The platelet counts from Oct 21 to 26, 1937 inclusive were made after the administration of 0.015 Gm of neoarsphenamine, before therapy with ascorbic acid, the counts from Jan 6 to 13, 1938 inclusive were made after the administration of 0.005 Gm of neoarsphenamine, after five days' therapy with ascorbic acid

neoarsphenamine Although this dose of the arsenical was only one third of the amount administered on Oct 21, 1937, the injection was scarcely completed before cyanosis, nausea, headache and rapid pulse developed Forty-five minutes after the onset of the reaction, a severe chill came on, for which 1 cc of epinephrine (1 1,000) was given subcutaneously The platelet count rose from 90,000 to 115,000 after the administration of the epinephrine at the one hour period after the administration of neoarsphenamine At the end of five hours the platelet count had dropped to 55,000, and purpuric lesions were appearing over the neck, the shoulders, the upper part of the chest and the extremities On account of severe prostration and the patient's senility, he was sent to the hospital for a period of twenty-four hours He recovered rapidly, by January 8, three days after he had received the neoarsphenamine, the platelet count was 320,000 per cubic millimeter

CASE 6—S H, a Mexican woman aged 45, had nausea, vomiting and headache after administration of 0.2 Gm of neoarsphenamine on Nov 20, 1937 On the following day purpura appeared over the arms, the upper anterior part

of the chest and both lower extremities. On December 3, 0.1 Gm of neoarsphenamine was administered intravenously for experimental production of thrombopenic purpura and to test her sensitivity to the arsenicals. An immediate reaction occurred, characterized by nausea, vomiting, rapid pulse, cold extremities and headache. The platelet count dropped to 80,000 at the end of thirty minutes after the injection, but rose again gradually, so that at the end of the two hour interval the count was 190,000 per cubic millimeter (table 6). On December 7 the platelet count was 240,000 per cubic millimeter, and the patient seemed to have recovered from her reaction.

On December 23 the patient was started on a regimen including daily oral dosage of 1 tablet of ascorbic acid, each tablet containing 100 mg. From December 29 to January 5 this intake of ascorbic acid was supplemented by daily intravenous injections of 100 mg of ascorbic acid. On January 5 the dose of 100 mg of ascorbic acid was injected intravenously, and, with the needle left in situ, a

TABLE 6—Data in Case 6

Date	Time	Platelet Count*	White Cell Count
12/3/37	Before administration of neoarsphenamine	270,000	8,500
	15 minutes after	160,000	6,200
	30 minutes after	80,000	7,600
	60 minutes after	130,000	8,100
	2 hours after	190,000	9,150
12/4/37	24 hours after	70,000	11,200
12/6/37	3 days after	140,000	9,800
12/7/37	4 days after	240,000	11,400
12/8/37	5 days after	270,000	10,300
1/5/38	Before administration of neoarsphenamine	360,000	10,200
	15 minutes after	240,000	7,100
	60 minutes after	70,000	6,200
	1½ hours after	80,000	7,050
	2 hours after	70,000	7,350
1/6/38	24 hours after	110,000	7,500
1/8/38	3 days after	300,000	10,000

* The platelet counts from Dec 3 to 8, 1937 inclusive were made after the administration of 0.1 Gm of neoarsphenamine, before therapy with ascorbic acid, the counts from Jan 5 to 8, 1938 inclusive were made after the administration of 0.075 Gm of neoarsphenamine, after fourteen days' therapy with ascorbic acid.

syringe was attached and 0.075 Gm of neoarsphenamine was administered immediately after the ascorbic acid. The reaction of the neoarsphenamine consisted of nausea, vomiting, rapid pulse, severe headache and prostration, and these symptoms began before all of the solution had entered the vein. One hour after the injection, the platelet count had dropped to 70,000 from 360,000 per cubic millimeter (table 6). At the end of two hours the bleeding time (Duke) was thirty minutes, and a purpuric eruption was becoming evident over the lower extremities. Twenty-four hours later the platelet count was 110,000. On January 8 the platelet count was 300,000. The patient felt somewhat weak, and purpuric lesions had spread to the neck, the shoulders, the arms, the upper part of the chest and the lower extremities. Clinically, the patient had recovered from the injection, but the purpuric eruption faded slowly.

Comment (cases 5 and 6)—Cases 5 and 6 can be commented on together, as the experiment in each instance was designed to test the hypothesis advanced by certain investigators, particularly by Giroud and Giroud,²² who reported that intravenous administration of 100 mg

22 Giroud, P., and Giroud, A. Influence du regime alimentaire sur la sensibilité du lapin à la sero-anaphylaxie, *Compt rend Soc de biol* 122 537, 1936.

of vitamin C to rabbits one-half minute to five minutes before the shocking dose of antigen gave almost complete protection against anaphylactic shock. In both cases 5 and 6 vitamin C was given for a few days previous to administering the dose, and from one-half minute to five minutes before administering the dose of neoarsphenamine. There was no diminution in the shock symptoms of these patients and no particular lessening of the degree of platelet drop and purpuric phenomena after vitamin C therapy, as compared with previous reactions which occurred when no preliminary vitamin C therapy had been instituted, and in each case smaller doses of neoarsphenamine were administered after vitamin therapy.

TABLE 7—Data in Case 7

Date	Time	Platelet Count*	White Cell Count	Plasma Vitamin C Content, Mg per 100 Cc of Blood
12/27/37	Before administration of neoarsphenamine	420,000	9,800	
12/28/37	Before administration of neoarsphenamine			0.81
12/29/37	Before administration of neoarsphenamine			0.84
12/30/37	Before administration of neoarsphenamine	460,000	5,600	
	15 minutes after	410,000	9,100	
	30 minutes after	490,000	9,100	
	60 minutes after	470,000	6,700	
	1½ hours after	480,000	7,200	
12/31/37	24 hours after	390,000	9,600	
1/ 3/38	Before administration of neoarsphenamine	340,000	11,300	
	15 minutes after	380,000	11,500	
	30 minutes after	330,000	11,900	
	60 minutes after	300,000	11,950	
		330,000	12,700	
8/ 2/39	Before administration of neoarsphenamine	290,000	11,100	
	15 minutes after	230,000	4,900	
	30 minutes after	150,000	5,100	
	60 minutes after	100,000	4,100	
8/ 3/39	24 hours after	200,000	9,300	

* The platelet counts for Dec 30 and 31, 1937 were made after the administration of 0.1 Gm of neoarsphenamine, after therapy with vitamin C, the counts for Jan 3, 1938 were made after the administration of 0.05 Gm of neoarsphenamine, after therapy with vitamin C, the counts for Aug 2 and 3, 1939 were made after the administration of 0.1 Gm of neoarsphenamine, with no vitamin C therapy.

CASE 7—J. L., an Italian aged 45, was 1 of 3 patients with thrombopenic purpura following neoarsphenamine therapy reported by us in 1936.²¹ He was hospitalized on Dec 27, 1937, so that the effects of vitamin C on his sensitivity to neoarsphenamine might be studied. The plan was to administer a dose of 0.1 Gm of neoarsphenamine to test his present sensitivity, then to administer vitamin C intravenously for about one week in an attempt to saturate the tissues. After one day in the hospital he informed us that he would not remain longer than December 31. On account of this short period for observation, no neoarsphenamine was administered until after the patient had received 300 mg of ascorbic acid intravenously. On December 30, 0.1 mg of neoarsphenamine was given intravenously, with the result that no untoward symptoms occurred after the dose and no significant decrease in the platelet counts took place (table 7). This was surprising, as he had previously been very sensitive to neoarsphenamine. The last dose received was on March 3, 1935. On Jan 3, 1938, after five days of no vitamin C intake except in his diet, the patient received a second dose of neoarsphenamine, 0.05 Gm. No reaction occurred and no purpura (table 7).

The number of platelets decreased only slightly. On Aug 2, 1939, after long search for this patient, he was located and induced to return for further testing relative to his sensitivity to neoarsphenamine. On this date he received 0.1 Gm of neoarsphenamine intravenously. There was no immediate reaction. After about one hour he had a chill and slight nausea. On the following day he felt normal. The platelet count fell considerably, but no purpuric lesions occurred (table 7). There had been no special vitamin C intake between the dates of Dec 30, 1937 and Aug 2, 1939, except that incidental to his diet.

Comment—This experiment is one of the most instructive and important of the series, for it shows how data may be misleading when the experiment is incomplete. Had we given only the two injections of neoarsphenamine, on Dec 30, 1937 and on Jan 3, 1938, we might have interpreted this patient's lack of a sensitivity reaction in each instance to the protective influence of the vitamin C. The mild reaction with no purpuric lesions on Aug 2, 1939 shows that he had experienced a loss of sensitivity to neoarsphenamine in the interval from March 3, 1935 to Dec 31, 1937. The two injections of neoarsphenamine, on Dec 31, 1937, and on Jan 3, 1938, served to increase his sensitivity to such an extent that it was still present on Aug 2, 1939, but much less in degree as compared with the reaction of March 3, 1935, when he had a prompt toxic reaction with purpura after the administration of 0.1 Gm of neoarsphenamine.

SUMMARY AND CONCLUSIONS

Attacks of experimental thrombopenic purpura following the administration of neoarsphenamine and bismarsen were repeatedly reproduced in 7 patients who were sensitive to one or the other or to both of these preparations.

Vitamin C in crystalline form as ascorbic acid, administered parenterally, orally and ingested in the diet, was given in varying amounts to these 7 patients, to determine whether it modified their sensitivity to the arsenicals or inhibited the occurrence of thrombopenic purpura following the administration of the arsenical responsible for their sensitivity.

It was found impossible to standardize the sensitivity reaction to a given amount of the arsphenamine preparation causing a reaction. The variation of the reaction to different amounts of the drug was marked in the same patient at various time intervals. Variation in the different patients of the series was considerable and appeared as a distinctly individual characteristic. At no time and in no patient observed was there any appreciable modification of sensitivity reaction during or after administration of vitamin C. The apparent increase in severity of the reactions after administration of vitamin C in certain of these patients was probably due entirely to increased sensitivity as the result of previously administered arsphenamine.

DERMATOMYOSITIS AND SYSTEMIC LUPUS ERYTHEMATOSUS

II A COMPARATIVE STUDY OF THE ESSENTIAL CLINICOPATHOLOGIC FEATURES

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In a previous publication an attempt was made to correlate the dermatologic and internal medical manifestations presented by a group of 5 cases illustrating what might be termed a "transitional" state between dermatomyositis and systemic lupus erythematosus¹ With but one exception, the cases were observed by me over relatively long periods, while the remaining instance provided an opportunity to furnish additional data on the early phases of the condition Besides these, other examples of dermatomyositis that have come under my observation were mentioned briefly in connection with the elaboration of certain fundamental points It is my belief that these diseases or manifestations of them will "become more common" when the practitioner learns to recognize them and their atypical variants, this is already apparent in the case of systemic lupus erythematosus It is interesting that the literature now contains the reports of hundreds of instances of dermatomyositis, many of these having been recorded under a variety of titles Though these diseases may, at times, present rather superficial resemblances to "rheumatism," they are unrelated to rheumatic fever in the precise sense in which that disease is understood today, and a vast number of postmortem observations appear to substantiate this view

Apart from the cases of "transitional" conditions, there are many other instances in which it is difficult, on clinical grounds at least, to differentiate systemic lupus erythematosus from dermatomyositis, especially when the patient is seen either very early in the course or in the later stages of the disease There are rare examples of the former condition that apparently fulfil all the clinicopathologic criteria for diagnosis and in which more or less marked involvement of the muscles is present, contrariwise, there are instances of the latter disease in which there are cutaneous manifestations that are differentiated with difficulty, if at all, from those associated with systemic lupus erythematosus Detailed

1 Keil, H. Dermatomyositis and Systemic Lupus Erythematosus. I. A Clinical Report of "Transitional" Cases, with a Consideration of Lead as a Possible Etiologic Factor, Arch Int Med 66 109 (July) 1940

studies of these syndromes reveal, however, that the average typical example of each disease ordinarily pursues a different course and in each individually peculiar internal medical features and fairly distinctive cutaneous lesions are present. Nevertheless, a considerable amount of overlapping does occur, as indicated in the case protocols previously detailed¹ as well as in others in the literature. Yet, there is, to borrow the words of Osler, "a positive advantage in recognizing the affinities and the strong points of similarity in affections usually grouped as separate diseases."

Among the clinical phenomena that may be encountered in both conditions are fever, pains of presumably articular nature, similar cutaneous and oral lesions, sensitivity to sunlight, Raynaud-like symptoms, lymphadenopathy, splenomegaly, leukopenia, a tendency to purpura, alopecia of the scalp, sterile cultures of blood, muscular involvement and renal disease. Both diseases may also run an afebrile course, and at times the clinical picture may be dominated by what may be called the sequelae of these conditions. Despite the apparent close similarities in features, these diseases may be differentiated if one pays close attention to certain clinical refinements. While these differences appear to warrant separation of the syndromes, it must be stressed again that the considerable overlapping of features suggests a closer relation between these conditions than has been generally accepted.

A CLINICAL DATA

1 *Age, Sex and Seasonal Incidence*—Systemic lupus erythematosus shows a striking predilection for young women, who often manifest unusual hypersensitivity to sunlight, but men may also be affected by this disease. Likewise, instances are encountered in children as well as in persons in the older age groups. Nevertheless, the vast majority of cases occur in young women, and, as the prognosis is poor, few of the patients seem to reach a mature age. The old dictum that lupus erythematosus does not occur in persons in the fifth decade and beyond because persons who would have had the disease then have already died from pulmonary tuberculosis cannot be substantiated by postmortem studies.² Of the two diseases, dermatomyositis is the more likely to occur in the male sex and appears, also, to be more common in older persons. There are, however, numerous instances in all age groups and in both sexes, so that a differential diagnosis based on these factors is hazardous. Likewise, the peculiarity of sensitivity to sunlight has been

2 Keil, H. (a) Relationship Between Lupus Erythematosus and Tuberculosis. A Critical Review Based on Observations at Necropsy, *Arch Dermat & Syph* 28 765 (Dec) 1933, (b) Conception of Lupus Erythematosus and Its Morphologic Variants, with Particular Reference to "Systemic" Lupus Erythematosus, *ibid* 36 729 (Oct) 1937.

recorded as occurring in many instances of dermatomyositis.³ As a corollary, both conditions are apt to have their clinical onset or exacerbation of symptoms between late spring and early autumn, though there are exceptions to this rule. The statement is often made that dermatomyositis is more likely to occur during the winter, but the records in the literature, when carefully analyzed, as well as my own observations, are at variance with this hypothesis. It is, however, true that in both conditions certain vasomotor phenomena, such as the Raynaud-like symptoms, may become particularly conspicuous with the advent of cold weather. This observation does not contradict the main thesis, for the vasculature in these patients may react to a variety of factors which, in view of the present state of knowledge, are to be regarded as predisposing agents rather than as the actual cause of the malady. Thus, I have observed several examples of superficial disseminated lupus erythematosus in which the illness had its apparent onset after exposure to sunlight or in which the patient was aware of previous sensitivity to this factor, yet in which subsequent exacerbations occasionally occurred during the cold weather.

2 Cutaneous Lesions—This subject will be discussed more fully in a succeeding publication. Here it is my intention, subject to the limitations previously stated, to mention some of the differential clinical points that tend to favor the diagnosis of dermatomyositis. These are (1) the early or initial involvement of the eyelids by a peculiar type of erythematous and telangiectatic edema, (2) the occurrence of special atrophic areas (soft and hard) over the small articulations of the fingers, occasionally about the larger joints and sometimes on the trunk, (3) the appearance of large areas of noncircumscribed erythema in relation to large masses of simultaneously affected muscles and subcutaneous tissue, (4) the occasional occurrence of an unusual degree of hypertrichosis, generally on areas the sites of previously inflamed subjacent structures, (5) the appearance of peculiar whitish areas in such places as the oral mucosa and the tongue, and (6) periungual and other changes.

As in the case of systemic lupus erythematosus,^{2b} there is often no precise correlation in dermatomyositis between the extent and intensity of the cutaneous lesions and the degree of muscular or internal visceral involvement. It is common to observe instances of both diseases in

3 (a) Turner, J. C. Dermatomyositis. A Study of Three Cases, *New England J. Med.* **216** 158, 1937. (b) Schuermann, H. Zur Klinik und Pathogenese der Dermatomyositis (Polymyositis), *Arch. f. Dermat. u. Syph.* **178** 414, 1939. (c) Dowling, G. B. Dermatomyositis, *St. Thomas Hosp. Rep.* **1** 150, 1936. (d) Towle, H. P. Dermatomyositis, *Arch. Dermat. & Syph.* **34** 298 (Aug.) 1936. (e) Witts, L. J. A Case of Dermatomyositis, *Brit. J. Dermat.* **48** 509, 1936. (f) Wanderer, E. Dermatomyositis, *Zentralbl. f. Haut- u. Geschlechtskr.* **53** 145, 1936. (g) Keil, H. Unpublished data.

which the manifestations in the skin may be overlooked or their significance underestimated, especially in cases in which mild changes appear. Conversely, there are occasional examples of both diseases, or allied syndromes, in which the cutaneous lesions either are apparently absent or occur relatively late in the course. Under such circumstances the diagnostic difficulties are enhanced, but there is considerable evidence that these cases are intimately related to those in which there is a striking eruption at the onset. In the past there has been much controversy regarding the classification of the condition in these instances, but detailed clinicopathologic studies have aided, at least in the case of systemic lupus erythematosus, in the formulation of criteria permitting recognition of instances of certain obscure syndromes temporarily or permanently deprived of the "revealing" cutaneous lesions. Among these may be mentioned

1 Cases of so-called rheumatoid arthritis in which there is sensitivity to sunlight, with subsequent or simultaneous involvement of the kidneys, the serous membranes and other parts ^{2b}

2 Cases of febrile thrombopenic purpura in which the cultures of blood are sterile and in which there occurs involvement of such organs as the kidneys. In a previous publication ⁴ I recorded the protocols of 2 such instances in which successful splenectomies for thrombopenic purpura were performed and in which the clinical picture of systemic lupus erythematosus subsequently appeared. Recently, a third example of the syndrome has come under my observation, and several other investigators have written to me regarding additional instances.

3 Peculiar examples of polyserositis with widespread involvement of other systems, including the renal tissue. This polyserositic form of systemic lupus erythematosus has been described by a number of observers, including Tremaine,⁵ Christian⁶ and Friedberg, Gross and Wal-

4 Keil, H. Relation Between "Systemic" Lupus Erythematosus and a Peculiar Form of Thrombocytopenic Purpura, *Brit J Dermat* **49** 221, 1937. The original draft of this paper was perused by both G. Baehr and P. Klemperer among others in 1933. At that time Baehr added annotations in which he claimed credit with Keil for knowledge of the capillary lesions in the syndrome described for the first time in this paper, and he excluded, intentionally and completely, the names of P. Klemperer and A. Schufrin. I did not include these annotations in the paper published in 1937. While Klemperer was not the first to discover the vascular lesions in the glomerular capillaries, especially in their relation to systemic lupus erythematosus, I feel that he deserves great credit for the descriptive name "wire-loop" lesions, used to describe these alterations in the kidneys.

5 Tremaine, M. J. Subacute Pick's Disease (Polyserositis) with Polyarthritis and Glomerulo-Nephritis. A Report of Two Fatal Cases, *New England J Med* **211** 754, 1934.

6 Christian, H. A. Long-Continued Fever with Inflammatory Changes in Serous and Synovial Membranes and Eventual Glomerulonephritis. A Clinical Syndrome of Unknown Etiology, *M Clin North America* **18** 1023, 1935.

lach⁷ among others, and I have had the opportunity of studying such instances, occurring with or without the appearance of the rash of lupus erythematosus. Examples of this syndrome in males have also come under my observation.

Just as the term systemic lupus erythematosus usually implies the simultaneous appearance of a typical rash, so the designation of dermatomyositis is generally reserved for instances in which there is implication of both skin and muscle. As in the case of the former disease, cutaneous manifestations may apparently be lacking in instances of dermatomyositis, if not permanently, at least temporarily, and here again there has arisen considerable debate regarding classification. When the rash is absent it is my custom to designate such examples as polymyositis (of such types as pure, hemorrhagic, fibrotic and calcific), there is considerable evidence indicating an alliance between many cases of these forms of disease and cases of ordinary dermatomyositis. Finally, there are a few other names that are occasionally met with in studying this disease, and it is proposed to complete this section by defining these terms.

1 *Dermatomucomyositis*. The oral lesions are emphasized by this term.

2 *Dermatoneuromyositis*. This name stresses the occasional secondary element of involvement of the small nerves situated in relation to the muscular bundles.

3 *Angiomyositis*. Originally this term referred to capillary dilatation as the presumable primary event in this disease. It has been used also in relation to the myopathies observed in the wake of arterial or venous disease of various types.

4 *Poikilodermatomyositis*. This name designates a form of dermatomyositis in which there occurs a reticulated type of pigmentation and in which muscular atrophy generally, but not always, appears in an insidious and often painless manner. The course is usually more chronic. These attributes are, however, inadequate to differentiate poikilodermatomyositis from ordinary dermatomyositis.

5 *Poikiloderma atrophicans vasculare*. Under this title numerous examples of poikilodermatomyositis have been recorded, in such instances either muscular disease has been overlooked, its significance depreciated or its clinical appearance much delayed. It is probable that Jacobi's original case⁸ of poikiloderma atrophicans vasculare was merely

7 Friedberg, C. K., Gross, L., and Wallach, K. Nonbacterial Thrombotic Endocarditis Associated with Prolonged Fever, Arthritis, Inflammation of Serous Membranes and Widespread Vascular Lesions, *Arch. Int. Med.* **58**: 662 (Oct.) 1936.

8 Jacobi, E. *Poikilodermia Atrophicans Vascularis*, in Neisser, A., and Jacobi, E. *Ikonographia dermatologica*. Berlin, Urban & Schwarzenberg, 1910, p. 95.

an unrecognized case of poikilodermatomyositis (dermatomyositis), the reasons for this view, as well as the entire subject of the poikilodermas, will be discussed in another publication

6 *Myositis fibrosa* This pathologic term refers to a common method of healing in instances of muscular diseases of various types. Some of the cases appear to belong in the category of dermatomyositis, as indicated by my study of the cutaneous manifestations and the general clinical features. This term creates difficulty only when it is used clinically to express the concept of a single disease instead of the pathologic end stage of many conditions, for example, the Jendrassik type of contracture.

7 *Scleroderma* Some observers, among them outstanding men like Dowling,⁹ have claimed that dermatomyositis is but one of the variants of scleroderma. It is my belief, however, that the resemblances are, on the whole, superficial and that these diseases should be sharply differentiated, despite occasional similarities in the clinicopathologic features.

8 *Suppurative polymyositis* This name refers to the frankly purulent or seropurulent forms of polymyositis observed in the course of various types of bacteremia. Confusion with ordinary dermatomyositis is likely only when thin seropurulent fluid is observed on sectioning of the muscles (for example, *Str. haemolyticus*), but minute anatomic study and culture generally differentiate them with ease. It is universally agreed that these conditions have little in common with dermatomyositis, except for occasional similarities in the clinical picture.

9 *Other forms of polymyositis* Involvement of muscles may sometimes be encountered after attacks of true scarlet fever, sinusitis, measles and many other diseases. The entire subject of the myopathies is sorely in need of fresh clinicopathologic studies, especially in regard to the unusual anomalies seen in association with the lymphoblastomas, and it appears that the musculature is affected in association with a larger number of conditions than is commonly suspected. This subject will receive additional consideration in the section concerned with the pathologic anatomy.

Nearly all the terms listed are probably superfluous and, perhaps, even confusing. Superfluous, because they tend to stress one feature at the expense of the others; confusing, because they add a multitude of names and syndromes. The term dermatomyositis, while perhaps not inclusive enough, emphasizes the chief diagnostic features of the syndrome, with the proviso that there are other variants and atypical clinical pictures to be included in this disease. Once the clinical picture of this condition is understood, the establishment of the diagnosis is fairly

⁹ Dowling, G. B. Two Cases of Dermatomyositis, *Proc. Roy. Soc. Med.* 31: 1357, 1938.

simple in the average case, only on the basis of such knowledge will it become possible, finally, to circumscribe the conception of the disease

3 *Disease in the Muscles*—The following discussion will be restricted chiefly to those instances in which there occurs involvement of the striated musculature, exclusive of the heart

(a) *Small Muscles* I have observed involvement of the interosseous and the small muscles of the hands in both systemic lupus erythematosus and dermatomyositis, this phenomenon appears to be more common in the latter disease, and especially in those cases showing a "transitional" state. Some observers believe that only the larger muscular masses in the proximal parts of the limbs are affected in dermatomyositis, but it is a view that admits of many exceptions. Indeed, practically any striated muscle in the body may be implicated in dermatomyositis, especially when the process is severe and widespread. In addition to the involvement of the small muscles in the hands, there is commonly seen in dermatomyositis involvement of the pharyngeal, laryngeal, intercostal, diaphragmatic and ocular muscles among others, and disease in these parts contributes significantly toward the evolution of a distinctive clinical picture. Involvement of these parts is especially important prognostically, as this factor is a direct or indirect cause of death, though it is probable that there may be occasional recoveries. Thus far, I have not encountered any typical example of systemic lupus erythematosus in which these small muscles were affected, at least to an extent sufficient to produce recognizable symptoms.

(b) *Large Muscles* Dermatomyositis is the disease par excellence in which the large muscular masses are chiefly affected, especially in the limbs. Increased opportunities for minute anatomic studies have led to the knowledge that practically any of the striated muscles may be involved in this disease. When, for example, the masseter muscles are affected, especially with concurrent implication of the subcutaneous tissue, the clinical picture of scleroderma may be closely simulated, and doubtlessly many examples of dermatomyositis have been classified in the category of scleroderma on the basis of such cursory similarities. In the chronic stage, occasionally early in the course, the secondary fibrosis occurring in parts near the joints or even in more remote areas may lead to the formation of contractures, in advanced phases of development the clinical picture is the counterpart of what is commonly described as myositis fibrosa. That in most instances there is excruciating pain on palpation of the muscles and the directly overlying tissues or on active or passive motion of the parts is well known, it is, however, not sufficiently appreciated that the factor of edema, which undoubtedly contributes significantly to the painful element, may be minimal, inconspicuous or altogether absent, and in such instances wasting of the

muscles may proceed in an insidious and often painless manner. In common with other observers, I have encountered in the course of ordinary systemic lupus erythematosus what may be termed "myalgic" phenomena, but I have not yet had the opportunity to submit such areas to the control of a minute anatomic examination. Not all the painful, edematous, reddened, deeply situated masses appearing in the limbs and accompanied by muscular swellings are examples of primary disease in the muscles, for I have seen a phlebitis in the arm of a patient with systemic lupus erythematosus simulate this appearance closely, similar phenomena associated with other conditions have been studied exhaustively by Lorenz and other observers.

In the section devoted to articular manifestations, the probable reason for the confusing of muscular and tendinous involvement with pains in the joints will be discussed. This phenomenon was understood by some observers over fifty years ago, but seems to have been forgotten or at least, its significance seems to have been underestimated.

Regarding the anatomic changes in biopsy specimens of muscles, there is a great deal of uncertainty as to what alterations are to be considered as significant, especially when these are minimal, and it must be admitted that absolute criteria have not yet been evolved. In every instance, however, the pathologic changes should be interpreted in terms of the clinical features, this is the only way in which it will become possible to evaluate such observations properly. There are many technical difficulties in evaluating the results of such examinations, and the subject of the myopathies needs enlightenment on the basis of more intensive and systematic studies in a variety of conditions, both abnormal and normal.

The evidence for the occasional collateral involvement of the skin and muscles in dermatomyositis will be reviewed in another publication.

4 *Involvement of Subcutaneous Tissue*—Although dermatomyositis is usually regarded as a disease affecting the muscles chiefly, the subcutaneous tissues are often implicated to a remarkable degree. In all likelihood, involvement of this structure contributes, partly at least, to the marked and often rapid wasting of many patients as well as to the doughy, firm, almost boardlike infiltrations regarded, when present, as characteristic of the disease. Whether the subcutaneous tissue is affected by direct continuity from the process in the muscles or whether the two areas are simultaneously involved by the same process is a question which cannot as yet be answered precisely. The histologic changes in the subcutaneous fat will not be discussed here, except for the statement that the vascular lesions and the *Wucheratrophie* encountered in many cases are probably not pathognomonic of a single disease. Systemic lupus erythematosus is usually free from such involve-

ment, except possibly in a few instances, but this conclusion cannot be stated confidently, for few studies have been concerned with this tissue Tremaine⁵ and others, including myself, have observed instances in which there was a rapid loss of weight, often disproportionate to the severity of the clinical features, but the exact nature of this phenomenon has not been determined, and it is probable that in systemic lupus erythematosus there are numerous factors accounting for such rapid loss of weight. In both diseases, but especially in dermatomyositis, it is common to encounter deep-seated, more or less transitory, edematous infiltrations in various parts of the body, generally in the subcutaneous tissue and easily differentiated from angioneurotic edema. In the fifth case of the previous report¹ this occurred in the cheeks, the situation and subsequent firmness suggesting scleroderma, the analogies were, however, only superficial. Calcific deposits may occur occasionally in the subcutaneous tissues in association with both conditions, and it appears that these are laid down in areas previously damaged, probably secondary to vascular disease or to the local intense edema of the parts. This phenomenon is also encountered in instances of scleroderma and probably other disease, in which the mechanism seems to be similar. The pathogenesis of these deposits may be contrasted possibly with that in idiopathic universal calcinosis, in which, according to the interesting observations of Bauer and his co-workers,¹⁰ calcium salts are deposited in tissues free from previous damage. Calcification in the muscles may be found occasionally in dermatomyositis, sometimes in cases of other diseases, I have not yet encountered this phenomenon in instances of systemic lupus erythematosus.

5 *Articular Involvement*—Patients afflicted with systemic lupus erythematosus often complain of pains in the joints. Usually these are of the nature of polyarthralgia, without definite evidence of intra-articular disease. It is probable that pathologic alterations will be found in the synovial membrane and the periarticular tissues, but exhaustive minute anatomic studies at this stage of the disease are lacking. In addition to cases in which this mild type of articular involvement occurs, there are instances of systemic lupus erythematosus in which the clinical findings in the joints seem to simulate early rheumatoid arthritis to such a degree as to render differential diagnosis difficult. In one such example Tremaine⁵ observed anatomic evidence of hypertrophy of the synovial villi, formation of subperiosteal bone and an inflammatory reaction in the periarticular tissue. It is not yet certain that the pathologic changes in rheumatoid arthritis are sufficiently distinctive

10 Bauer, W., Marble, A., and Bennett, G. A. Further Study in a Case of Calcification of Subcutaneous Tissue ("Calcinosis Universalis") in a Child, *Am J M Sc* 182 237, 1931.

to allow an etiologic classification on that basis. Thus far, I have not encountered cases in which the typical ulnar deviation of more or less advanced rheumatoid arthritis was present, though I have observed several instances in which there were marked periarticular thickenings in the fingers, knees and other parts. As was previously stated, such cases are differentiated from instances of the ordinary type of rheumatoid arthritis by unusual sensitivity to sunlight and ultraviolet rays, renal disease, involvement of various serous membranes, a typical rash and other features, and for patients with such symptoms gold salts should be administered with the utmost circumspection, certainly not in large doses. When the collateral evidence is lacking or, perhaps, overlooked, the early diagnosis of systemic lupus erythematosus is not likely to be made. In my own observations, these cases have always concerned members of the female sex, but it is probable that exceptions will be found. Except rarely, the atrophy in the interosseous muscles and the muscles in the thenar and hypothenar eminences was entirely out of proportion to the severity of the subjective symptoms and the objective signs in the small joints of the hands, in most instances under my observation articular pains were minimal or altogether absent.

Dermatomyositis generally spares the joints, at least in a pathologic sense. There are, however, patients who complain of pains that seem to be about or near the articulations, but it is likely that in such instances the deeper tendons, the terminal portions of the muscles or even the subcutaneous tissues in this general region will be found to be implicated by a vascular, inflammatory or edematous process or by combinations of the three. Over fifty years ago Hepp¹¹ and others said that they recognized that disease in the tendinous portions of the muscles is often responsible for the pains about the joints, and while there is no abundance of anatomic protocols to prove the point, this seems likely when one considers the clinicopathologic features closely. Such pains may possibly also arise in connection with secondary involvement of the nerve endings in widespread disease of the muscular parenchyma, this phenomenon, the significance of which is difficult to assess, is probably uncommon.^{11a} In this respect dermatomyositis seems to contrast with periarteritis nodosa, a disease that may at times show analogous clinical features. In periarteritis nodosa involvement of the nerves, which is generally found to be secondary to disease in the arteries supplying these structures, produces the clinical picture of a true neuritis,

11 Hepp, P. Ueber Pseudotrichinose, eine besonderer Form von acute parenchymatöser Polymyositis, *Berl klin Wchnschr* **24** 297, 1887.

11a In an interesting paper Kellgren (Kellgren, J. H. Observations on Referred Pain Arising from Muscles, *Clin Sc* **3** 175, 1938) found that pain in the muscles of the limbs is often referred to joints or deeply near joints, hence, true articular pains may be simulated by this mechanism in some instances.

with all the usual accompanying signs, including the reaction of degeneration to the electrical current. The status of cases of so-called intermediary conditions is debatable and will not be discussed here, it may be said, however, that with but rare exceptions the clinical picture of the average example of dermatomyositis is vastly different from that of periathritis nodosa.

While there is no clinical evidence of genuine involvement of joints in dermatomyositis, there are encountered, on the other hand, articular deformities due to contracture produced by fibrosis of the parts already mentioned. These contractures are generally observed in well established conditions, but occasionally they may occur surprisingly early in the course. In the end stages the clinical picture of myositis fibrosa is produced. The observation of such cases is the basis of my belief that many instances of so-called myositis fibrosa represent merely the terminal phases of chronic dermatomyositis or a related syndrome. This belief is, moreover, bolstered by a study of the cutaneous lesions associated with the disease, for example, Blau's first patient,¹² whom I had the opportunity to observe, showed the typical patches over the small joints of the hands and in the other usual sites. Blau stressed the point that the contractures in his 2 cases of myositis fibrosa were not the result of articular disease, but were rather the sequel of tension in the tendons opposing movements in the joints. As far back as 1888 Jacoby¹³ made a similar observation in reporting his case of polymyositis, and many others have emphasized this point, which often seems to be overlooked clinically, on a number of occasions I have seen examples of this disease labeled as rheumatoid arthritis. In cases of dermatomyositis such contractures are observed chiefly about the elbows, knees, hips and fingers. I cannot recall having seen a similar phenomenon in instances of systemic lupus erythematosus aside from a moderate stiffness in the knees and in the finger joints proper, simulating the clinical picture of rheumatoid arthritis closely. In occasional instances of dermatomyositis there may be rarefaction of the bones in the neighborhood of joints as shown by roentgenograms, the precise genesis of this condition is unclear at present.

6 Renal Disease—Systemic lupus erythematosus affects the kidneys in such a high percentage of cases that this feature may be regarded, with considerable justification, as an integral part of the disease. The urinary findings are comparable with those observed in "inflammatory nephritis", occasionally gross hematuria is present. However, micro-

12 Blau, A. Primary Generalized Myositis Fibrosa. Report of Two Cases with Histopathology, *J Mt Sinai Hosp* 5 432, 1938.

13 Jacoby, G. W. Subacute Progressive Polymyositis, *J Nerv & Ment Dis* 15 697, 1888.

scopic examination of the kidneys post mortem shows that the major changes are nearly always dependent on vascular disease in the capillary loops in the glomeruli ("wire-loop lesions," "hyaline thrombi"), sometimes on that in the larger vessels on both the arterial and the venous side, in some instances, also, there is additional involvement in the nature of "glomerulonephritis" of restricted or more widespread distribution. The clinicopathologic significance of these lesions will be discussed later in connection with the vascular concept of this disease.

Early in the clinical course examination of urinary specimens may reveal no abnormalities, from which it may be supposed that the renal tissue is spared. This I have observed on a score of occasions, yet it is difficult to be certain in all instances that these organs were really free from disease. On the other hand, I have encountered a number of cases in which the cutaneous phase antedated the systemic phase by as long as from one to two years or more. Postmortem correlation indicates that in other cases, at least, the kidneys may be affected in a subclinical fashion, so to speak. At necropsy it is common to observe gross evidence of closure of small vessels in many instances, if a careful examination is made. There are, however, other cases in which the gross appearance of these organs seems to be normal, yet minute anatomic studies reveal important vascular alterations. In the days before this was sufficiently appreciated, the kidneys were often discarded, with the result that these vascular changes were overlooked or were observed so infrequently as to occasion little curiosity regarding their possible significance. In most instances the observer may expect to find these alterations when examinations of urinary specimens show formed elements, including red blood cells, but it must be stressed that the vascular changes may be minimal and sometimes absent. Often the glomeruli are affected in what seems to be a patchy distribution. Azotemia is usually of moderate grade because as it has been stated, the lesions are irregularly distributed and because these patients often succumb prematurely to a complicating disease such as bronchopneumonia. There are, however, occasional instances showing marked nitrogen retention approximating that associated with uremia, and the clinical picture of the latter may occasionally be simulated¹⁴. In such examples, also, the specific gravity of the urine may be fixed at 1.010. The superimposition of terminal bacteremia, with the formation of abscesses in the kidneys, is one of the most likely causes in the production of a grade of azotemia comparable to that occurring in uremia.

¹⁴ Keil, H. The So-Called Libman-Sacks Syndrome, *Arch. Dermat. & Syph.* **34** 124 (Jan.) 1936, in discussion on Osler, W. On the Visceral Manifestations of the Erythema Group of Skin Diseases (cases 19 and 26), *Am. J. M. Sc.* **127** 1, 1904, footnote 2 b.

On the other hand, there are numerous cases in which the features of nephrosis or of the nephrotic phase of glomerulonephritis may be simulated, owing to the following causes 1 A tendency to, or actual, inversion of the albumin-globulin ratio The total protein may be somewhat diminished, or, if the content of globulin is increased, as sometimes occurs, the total content of protein may be within normal limits 2 A slight increase in the amount of cholesterol in the blood Extreme hypercholesteremia, such as that often encountered in instances of nephrosis or the nephrotic phase of glomerulonephritis, I have but rarely observed in cases of systemic lupus erythematosus In other instances the cholesterol value is normal or even diminished, and this is sometimes observed even in association with a diminished total value for protein and with a tendency to inversion of the albumin-globulin ratio 3 The occurrence of edematous collections of fluid in various parts of the body, especially the serous cavities 4 A moderate or slight increase in blood pressure In occasional instances extreme hypertension may be found The variations in the blood pressure will be discussed conveniently at the end of this section for purposes of contrasting this phenomenon with that occurring in cases of dermatomyositis In any event, there is usually no particular difficulty in distinguishing the nature of the renal changes in systemic lupus erythematosus from that of the alterations in other types of degenerative, inflammatory or vascular diseases in the kidneys, provided the entire clinical picture is taken into consideration and judged on the basis of previous postmortem observations

In some instances of systemic lupus erythematosus the globulin value in the blood seems to be somewhat elevated, but according to the cases under my observation this characteristic is not constant The point will be referred to again in the section concerned with serology

In a consideration of dermatomyositis the data are more difficult to evaluate for at least two reasons (1) the inclusion of cases showing "transitional" features and (2) the pitfalls created by drawing conclusions on the sole basis of the findings in urinary examinations Oppenheim¹⁵ stated that nephritis is a common complication in cases of dermatomyositis, but he did not offer adequate evidence to substantiate this thesis, nor did he define what he meant by nephritis, though it is to be presumed that he was speaking of the inflammatory type In Korniloff's case,¹⁶ the status of which is debatable, the patient had glomerulonephritis, but whether this was coincidental remains controversial In most of the few cases cited as showing evidence of

15 Oppenheim, H Lehrbuch der Nervenkrankheiten, ed 7, Berlin, S Karger, 1923 vol 1, p 840

16 Korniloff, A A Polymyositis primaria acuta, Deutsche Ztschr f Nervenhe 9 119, 1896

nephritis, the urinary specimens contained a variable amount of albumin, with occasional casts,¹⁷ sometimes such findings seemed to be correlated with a febrile state, but in other instances this explanation appeared not to be applicable. In Fahr's case,^{17c} for example, an examination of urine performed late in the course showed albumin, casts and white blood cells, yet the kidneys post mortem were apparently free from significant alterations. In the protocols recorded by Steinitz and Steinfeld¹⁸ and by Schill¹⁹ mention was made of the appearance of a few red blood cells in the urine, in these instances the findings seemed to be correlated best with the factor of cardiac failure accompanied by chronic passive congestion in the kidneys.

There are a few recorded instances of dermatomyositis in which gross hematuria was encountered. This was also noted in cases 2 and 5 described in my previous report.¹ In case 2 the hematuria seemed to be part of a generalized bleeding tendency that manifested itself at the time, a similar occurrence was also noted by Schuermann.^{3b} In Batten's²⁰ patient painless hematuria appeared, but at postmortem examination this was discovered to be caused by a stone in the ureter. Koster²¹ recorded the occurrence of hematuria in 1 instance, but this case was probably an unusual example of the Henoch-Osler-Schonlein group, and, indeed, Koster was not certain of the precise classification of that case. Critical analysis of recorded data, therefore, shows how difficult it is to draw absolute conclusions in the absence of a carefully performed postmortem examination. Except in rare instances,^{17d} there is usually no impairment in the concentrating power of the urine. In the unusual example described by Talbott and his co-workers,²² the urinary specimens collected early in the course showed no abnormalities.

17 (a) Sydenstricker, V. P., and Thomas, D. R., Jr. Dermatomyositis. *Ann Int Med* **8** 959, 1935. (b) Senator, H. Ueber acute und subacute multiple Neuritis und Myositis, *Ztschr f klin Med* **15** 61, 1889. (c) Strumpell, A. Zur Kenntnis der primären acuten Polymyositis, *Deutsche Ztschr f Nervenh* **1** 479, 1891. (d) McLester, J. S. Dermatomyositis, *Tr A Am Physicians* **41** 283, 1926. (e) Fahr, T. Zur Frage der Polymyositis (Dermatomyositis), *Arch f Dermat u Syph* **130** 1, 1921. (f) Hepp.¹¹

18 Steinitz, H., and Steinfeld, F. Untersuchungen zum Creatin-Stoffwechsel bei Dermatomyositis, *Ztschr f d ges exper Med* **79** 319, 1931.

19 Schill, E. Ueber einen Fall von Polymyositis, *Wien Arch f inn Med* **12** 353, 1926.

20 Batten, F. E. Case of Dermatomyositis in a Child, with Pathological Report, *Brit J Child Dis* **9** 247, 1912.

21 Koster, H. Zur Kenntnis der Dermatomyositis, *Deutsche Ztschr f Nervenh* **12** 150, 1897-1898.

22 Talbott, J. H., Gall, E. A., Consolazio, W. V., and Coombs, F. S. Dermatomyositis with Scleroderma, Calcinosis and Renal Endarteritis Associated with Focal Cortical Necrosis. Report of a Case in Which the Condition Simulated Addison's Disease, with Comment on Metabolic and Pathologic Studies, *Arch Int Med* **63** 476 (March) 1939.

in the specific gravity or in formed elements, yet one week before death the specific gravity became fixed at 1.010 and the postmortem examination seemed to explain this feature satisfactorily, for there was observed a remarkably widespread subintimal proliferative lesion in the interlobular arteries in the kidneys, with secondary effects on the renal parenchyma. Even in this case blood was apparently not present in the urine.²³

The few cases in which there was the most definite clinical evidence of renal damage appeared to be the ones in which the condition resembled systemic lupus erythematosus closely, for example, the instance recorded by Weber and Gray.²⁴ As the patient in this case recovered, the point could not be definitely substantiated by minute anatomic studies. In any event, such cases are uncommon. In Lane's²⁵ case the urinary specimens showed no abnormalities, yet there was a definite tendency to reversal in the albumin-globulin ratio, chiefly due to an increase in the globulin fraction, with a cholesterol value that was, perhaps, slightly increased. It is probable that in some instances the albumin fraction may be diminished owing to widespread loss of protein in the edematous fluid that is poured out into the muscular and subcutaneous tissues in dermatomyositis. It is doubtful whether the kidneys of Lane's patient were damaged, it is possible, however, as is the case in systemic lupus erythematosus, that urinary findings may be normal for varying periods. A follow-up study of such cases is therefore an essential part of the study.

Both diseases may be attended occasionally by a moderate degree of hypertension. In rare cases the rise in blood pressure may be marked. According to my observations, this phenomenon is more likely to be encountered in cases of systemic lupus erythematosus, owing chiefly to widespread involvement of the glomerular capillaries, and, perhaps, to superimposed infarction or simultaneous glomerulonephritis. It cannot, however, be said that the anatomic changes can be precisely correlated with the degree of hypertension, and it seems probable that extraneous factors sometimes enter, for example, the superimposition of abscesses in the kidneys owing to complicating bacteremia. I have encountered several instances of systemic lupus erythematosus in which the clinical

23 The status of the case recorded in footnote 22 is not entirely clear. The vascular lesions described by these authors are similar to those recorded in a few examples of scleroderma. This case is interpreted best, in my view, as one of scleroderma with secondary and concomitant muscular changes. Yet, because it is difficult to be certain, it may be more reasonable to regard the condition as subjudice.

24 Weber, F. P., and Gray, A. M. H. Chronic Relapsing Polydermatomyositis with Predominant Involvement of the Subcutaneous Fat (Panniculitis), *Brit. J. Dermat.* **36** 544, 1924.

25 Lane, C. W. Dermatomyositis, *South. M. J.* **31** 287, 1938.

features simulated the nephrotic phase of glomerulonephritis, with moderate elevation of the blood pressure,²⁶ indeed, in 1 case under my observation the nature of the condition was misunderstood because of failure to evaluate the significance of the eruption that had been present at the time of the patient's previous admissions. When the cutaneous lesions fade, as they often do in the terminal phases, the diagnosis becomes more difficult, and in such cases the postmortem observations assume great importance. It must be stressed that in the average example of systemic lupus erythematosus an appreciable elevation in the blood pressure generally does not occur, nevertheless, hypertension does occur for various reasons, and I can therefore substantiate the observations of Rose and Pillsbury,^{26a} who reported a number of such examples of systemic lupus erythematosus.

In occasional cases of dermatomyositis there is a moderate elevation in the blood pressure. Thus, Fahr^{17c} recorded the protocol of 1 such instance and, as the kidneys were apparently free from significant alterations, he was inclined to attribute the hypertension to the occurrence of widespread arterial disease in the muscles. I have encountered 1 example of dermatomyositis in which the blood pressure became more elevated and reached a level of 200 mm systolic with a correspondingly increased diastolic pressure, here again, the renal findings were apparently insufficient to explain the phenomenon, supporting to a certain extent the conclusion reached by Fahr. Yet it is extremely common to encounter instances in which widespread muscular disease is present, with or without what one might call pronounced vascular changes, and the blood pressure maintains itself at a normal level. Why hypertension occurs in some instances and whether it is related to the type of vascular alteration observed in the arteries in the muscles are questions to which the present knowledge fails to provide satisfactory answers. It is even possible that the 2 cases of hypertension just discussed may have been coincidental in the sense of having a complicating essential hypertension in the early stages. In the case reported by Talbott and his associates,²² in which there occurred marked changes in the interlobular arteries with partial necrosis of the renal parenchyma, there was no rise in blood pressure, on the contrary, the outstanding feature was a "postural hypotension," which was regarded as evidence supporting the original diagnosis of Addison's disease.²³

In general, then, the clinicopathologic features are in harmony with the observations on the blood pressure, and the evidence indicates that the kidneys are, as a rule, spared in dermatomyositis.

26 (a) Rose, E, and Pillsbury, D M. Acute Disseminated Lupus Erythematosus. A Systemic Disease, *Ann Int Med* **12** 951, 1939. (b) Keil^{3g}
 (c) Tremaine⁵ (d) Friedberg, Gross and Wallach⁷

7 *Ophthalmoscopic Observations*—In systemic lupus erythematosus the fundi often reveal alterations. The evidence appears to indicate that these changes arise primarily in relation to the blood vessels and that they represent but one of the manifestations of a systemic disease. Their occurrence cannot be precisely correlated with the severity of the clinical course, nor can any deductions be made regarding the immediate prognosis. In general, however, such changes may be regarded as another evidence that the condition has become systemic. Ophthalmoscopic examination reveals in most instances that the hemorrhages and soft (fluffy) exudates are arranged in general in a perivascular fashion. It is doubtful whether such appearances are pathognomonic of systemic lupus erythematosus. In view of the fact that the blood pressure is usually within the limits of normal and in view of the nature of the data on the other manifestations of the disease (for example, embolism is extremely unlikely, and blood cultures are sterile), it seems reasonable to conclude that the lesions are of local origin. Furthermore, it is likely that the pathologic alterations will be found to be analogous to those seen in other organs, in all probability the exudates noted are simply collections of edematous fluid, with properties similar to those exhibited by the edematous fluid in the upper part of the corneum skin. Peripapillary edema of varying severity occurs more commonly than is generally suspected, of this phenomenon I have seen 3 striking examples, and I have notes on several others. In the case of this anomaly too, knowledge of the other features of the disease would lead me to believe that this is dependent on vascular damage, with the "transudation" of edematous fluid in relation to the papilla. There is no evidence that this type of papilledema is caused by an increase in the intracranial pressure or by such pressure as that on the large structures in the eyeball. In nearly all the instances under my observation the patient recovered from the immediate attack, the changes in the eyegrounds subsiding completely. Such periods of spontaneous resolution are merely more or less prolonged remissions in a condition that, according to my observations, eventually suffers a recrudescence with fatal issue. Goldstein and Wexler²⁷ recorded an unusual case of atrophy of the optic nerves associated with alterations in the retinal arterioles chiefly, and they showed definitely that the areas of punched-out atrophy seen ophthalmoscopically were related probably to the pathologic changes in the vessels in the retina, as contrasted with the chorioretinitis observed in instances of "sepsis." This case, which I had the opportunity of studying many years ago, is unique in the occurrence of bilateral atrophy of the optic nerves, but the relation of this finding remains unclarified in my mind in view of the fact that at the

27 Goldstein, I, and Wexler, D. Retinal Vascular Disease in a Case of Acute Lupus Erythematosus Disseminatus, *Arch Ophth* 8:852 (Dec) 1932

same time the spinal fluid showed a colloidal gold curve of the paretic type²⁸ In any event, Goldstein and Wexler deserve great credit for their thorough pathologic studies, which showed that the major changes were of retinal origin Abramowicz and Dulewicz²⁹ recorded the occurrence of oval edematous foci in the fundus of a patient afflicted with acute lupus erythematosus and stated that these resembled "retinitis guttata" as described by Dimmer in association with arteriosclerosis and other diseases of unknown cause, however, no pathologic studies were made On the other hand, Semon and Wolff³⁰ described a few round, slightly raised, whitish areas in the disks occurring in a case of fatal systemic lupus erythematosus, these lesions bore only a superficial resemblance to choroidal tubercles Microscopic examination revealed that the major alterations were in the choroidal layer, with a well marked subretinal inflammatory exudate showing a tendency to repair In this instance the patient complained of misty vision Recently, Klauder and Ellis³¹ observed a man aged 36 years who was afflicted with systemic lupus erythematosus of relatively short duration, early in the course the patient complained of blurring of vision Ophthalmoscopic examination revealed various-sized, fluffy, cloudlike patches throughout the fundus, especially around the disks, with a few small hemorrhages around the macula The visual acuity was 3/60 in each eye In the discussion of this case, Lillie stated that he regarded the changes as those of diffuse perivasculitis and periphlebitis

Despite fairly extensive changes in the fundi, it is uncommon to encounter patients who complain of subjective symptoms of visual disturbances, such as haziness of vision In addition to the case described by Goldstein and Wexler, I have observed 1 other example in which there was blindness, attributed to an "embolism" of the central retinal artery with secondary glaucomatous change in the affected eye As this followed an intravenous injection of a gold compound, it seems difficult to be certain of the precise genesis, though it seems possible that this might have been due to a local vascular closure

Finally, Pillat³² observed choroidal foci in the peripheral portions of the fundus at sites of slowing of the circulation, these changes were probably old, as indicated by the presence of a peripheral ring of pig-

28 Records of the Mount Sinai Hospital, New York City, Postmortem 7762, May 7, 1931 (A K)

29 Abramowicz, I, and Dulewicz, M Le fond de l'oeil dans le lupus erythematosus acutus (erythema perstans), Ann d'ocul **170** 599, 1933

30 Semon, H C, and Wolff, E Acute Lupus Erythematosus with Fundus Lesions, Proc Roy Soc Med **27** 153, 1933

31 Klauder, J V, and Ellis, V M Effective Treatment of Lupus Erythematosus and Exudative Retinitis with a Gold Compound, Arch Ophth **21** 893 (May) 1939

32 Pillat, A Ueber das Vorkommen von Chorioiditis bei Lupus erythematosus, Arch f Ophth **133** 566, 1935

mentation In most of the cases these patches were unilateral, and in 2 instances there were fresh alterations These areas of choroiditis were encountered in one third of 48 examples of lupus erythematosus, and on the basis of their attributes, though atypical in some respects, Pillat said that he was inclined to attribute them to tuberculosis In 4 instances also, there were old changes in the cornea (*keratitis eczematosa*), residues of an old process which probably had its onset in youth Pillat stressed the asymptomatic nature of these findings It is evident, from a perusal of his report that there was no precise relation between these lesions as described and the nature of the lupus erythematosus, except, perhaps, in 2 of the cases, and even in these instances there is room for considerable doubt Furthermore, the nature of these choroidal changes becomes even more debatable when it is found that Pillat³³ observed similar lesions in 60.7 per cent of 28 cases of acute polyarthritis If one assumes that these changes were of tuberculous nature, which seems likely, it becomes clear that this is additional evidence for believing that the population of Vienna is, or was, heavily infected with tuberculosis (*morbus viennensis*)

The alterations previously mentioned as occurring in systemic lupus erythematosus have not yet been submitted to thorough microscopic examination These changes, as has been indicated, are capable of complete restitution to normal, at least temporarily, and it is likely that any pigmentary disturbances in such areas would be dependent on the extravasation of blood pigment (positive iron stain) Such lesions, furthermore, seem not to acquire a peripheral ring of pigmentation

In cases of dermatomyositis ophthalmoscopic examinations generally reveal no abnormalities, though there are exceptions to this rule In comparison with those associated with systemic lupus erythematosus changes in the fundi are comparatively uncommon In this respect dermatomyositis seems to behave more like a localized disease than does systemic lupus erythematosus In 1933 Gronblad³⁴ made an interesting contribution in a paper describing the ocular lesions in 3 cases of poikilodermatomyositis, a condition that appears to be identical with ordinary dermatomyositis Gronblad recorded the following observations: the occurrence of edema localized to the peripapillary region, these changes being apparently situated deeply, without definite relation to the retinal vessels, peripheral isolated round spots which seemed to lie in the neighborhood of fine retinal vessels and which he interpreted as atrophic, edema of the vitreous at the macula, similar to the peripapillary edema, and in 1 case the appearance of a small hemorrhage that disappeared in two weeks Visual acuity was normal Gronblad noticed

33 Pillat, A. Ueber Augenhintergrundsbe funde bei akuter Polyarthritis, *Wien klin Wchnschr* 48 303, 1935

34 Gronblad E. Des alterations oculaires dans la poikilodermatomyositis, *Acta ophth* 11 461, 1933

that in 2 of the 3 cases it was difficult to dilate the eyes, a circumstance which he thought was attributable to muscular disease. Ocular disease involving the small muscles of the eyes is encountered occasionally in cases of dermatomyositis, it is probably extremely rare in those of ordinary systemic lupus erythematosus. Recently, Bruce³⁵ recorded the occurrence of "retinitis" associated with 3 interesting examples of dermatomyositis, 2 of these concerning children. Of the patients in this group 2 recovered, despite extensive changes in the fundi. In all the patients the retinal veins were somewhat distended, occasionally indented by arteries that were normal in appearance. Scattered throughout the fundi were varying numbers of grayish yellow exudates that seemed, for the most part, to be superficially located and resembled the "cotton-wool" exudates of albuminuric retinitis, some of the smaller areas were apparently deeper in situation and simulated choroidal tubercles (case 2). Some of the exudates were in relation to the maculas (cases 1 and 2), while in 2 instances there was slight haziness of the disk margins (cases 2 and 3). In all 3 instances there were superficial or deeper hemorrhages, generally lying along the course of veins. The second patient in the group complained of dimness of vision, but the severity of the illness or the age of the subjects prevented Bruce from obtaining data on the visual acuity and fields. The patient in case 1, a girl of 11 years, died, microscopic examination of the posterior poles of the eyes revealed edematous and hemorrhagic changes in the retinal layers, but postmortem changes obscured many of the finer details. In any event, the alterations described were in harmony with the clinical findings. The observations recorded by Bruce seem to be similar to those just described in the section on systemic lupus erythematosus. In this connection it is pertinent to say that I once observed an instance of hemorrhages and exudates in the fundus of a patient who complained of severe pains in the muscles and subcutaneous tissues, the course was rapidly fatal, and postmortem examination revealed possible lymphatic leukemia of an atypical type.

It will be seen, then, that the changes in the fundus oculi, probably of a nonspecific nature in a clinical sense, are observed with regularity in cases of systemic lupus erythematosus and less commonly in those of dermatomyositis and its clinical congeners.

8 *Cardiac Involvement*—(a) Endocardial Disease. In a considerable percentage of cases of systemic lupus erythematosus, roughly in from 30 to 50 per cent, there occurs gross evidence of pathologic changes in the endocardium, both valvular and mural. Credit is due Libman and Sacks³⁶ who in 1923-1924 first clearly recognized atypical

³⁵ Bruce, G. M. Retinitis in Dermatomyositis, *Tr. Am. Ophth. Soc.* **36** 282, 1938.

³⁶ Libman, E., and Sacks, B. A Hitherto Undescribed Form of Valvular and Mural Endocarditis, *Arch. Int. Med.* **33** 701 (June) 1924.

verrucous endocarditis, which they found in 4 cases. The patients in these cases showed clinical features simulating both rheumatic fever and subacute bacterial endocarditis, yet differing in many respects from these two conditions. In 2 of their cases there were observed eruptions that the consulting dermatologist was unwilling to identify as lupus erythematosus, but current knowledge indicates that undue stress was laid on obsolete criteria. In 1930 I recognized that systemic lupus erythematosus may occur without gross endocardial changes post mortem ^{36a}. Earlier in that year there came under my observation an instance of systemic lupus erythematosus in which the occurrence of atypical verrucous endocarditis was diagnosed correctly, yet at post-mortem examination the endocardial changes appeared too slight to have occasioned conspicuous clinical signs of valvular disease. In 1932 Gross ³⁷ recorded an outstanding study of the pathologic anatomy of atypical verrucous endocarditis, with particular reference to the valvular alterations and the vascular changes in the myocardium. Of special importance was his description of the "pocket lesions" in this condition. The microscopic features in this type of endocardial disease as observed in the valves, the chordae tendineae and the mural portion of the endocardium, the tendency to involve the right side of the heart, often to the exclusion of the left side and other characteristics of the condition, were described by Gross in great detail ³⁸.

There is ample evidence that this variety of cardiac disease is not related directly to that seen in cases of rheumatic fever, ^{38a} although the

36a In a paper by Baehr (Baehr, G. Renal Complications of Endocarditis, *Tr A Am Physicians* 46:87, 1931) mention was made of 2 cases of systemic lupus erythematosus without gross valvular changes. These examples, which were not included in the statistics, were given to Baehr by me in a list of cases that I had gathered in 1930 from the records of the Mount Sinai Hospital. These cases as well as many others on the list had been buried in the records under a wide variety of diagnoses. Also, the section of skin demonstrated at the meeting of the association had been sectioned and stained by me.

37 Gross, L. The Heart in Atypical Verrucous Endocarditis (Libman-Sacks), in *Contributions to the Medical Sciences in Honor of Dr Emanuel Libman by His Pupils, Friends and Colleagues*, New York, International Press, 1932, vol 2, p 527.

38 Gross, L. The Cardiac Lesion in Libman-Sacks Disease with a Consideration of Its Relationship to Acute Disseminated Lupus Erythematosus, to be published, manuscript and revisions in possession of Dr E Libman New York.

38a A few cases of systemic lupus erythematosus are complicated by acute bacterial endocarditis, rarely by subacute bacterial endocarditis. These complications occur probably late in the course of the disease and in all likelihood are not an essential part of it. I have seen an instance of discord atrophic lupus erythematosus in a patient with rheumatic heart disease, confirmed at necropsy, the two conditions were probably coincidental and unrelated. Every case of endocardial lesions must therefore be evaluated critically on the basis of a knowledge of the various types of endocardial changes seen in association with this disease.

occasional association of chronic valvular alterations still requires clarification. There are, moreover, occasional instances in which the body of the valves, generally the mitral or the tricuspid valve, shows evidence of an inflammatory process that, according to Gross, may be differentiated from rheumatic valvulitis by the local pathologic features and the general sparing of the ring, when, as may happen occasionally, the ring is invaded by systemic lupus erythematosus, the changes are still distinguishable from the characteristic lesion in rheumatic heart disease. These statements are based on the microscopic criteria elaborated by Gross³⁸

Notwithstanding the nosologic importance of atypical verrucous endocarditis, it seems probable that the area of distribution of these verrucae and the manner in which they are deposited contribute but little to the signs and symptoms in this disease. Most of the audible murmurs are, in all likelihood, attributable to extraneous factors, except in the relatively uncommon cases in which old valvular changes are encountered. The simultaneous occurrence of a pericardial rub makes the existence of gross endocardial involvement more probable, as these two parts of the cardiac structure are often concurrently affected, but this rule has exceptions.⁴¹ In a succeeding paragraph an attempt will be made to evaluate the significance of nonbacterial thrombotic endocarditis as described by Friedberg, Gross and Wallach,⁷ for this subject seems destined to have some relation to systemic lupus erythematosus.

In typical instances of dermatomyositis the endocardium seems to be spared, except possibly in occasional cases. Thus, Potain³⁹ described a slight marginal thickening in the mitral valve, apparently of recent origin, as it was red and showed deposition of small granulations on the surface (fibrinous, nonadherent). The nature of the endocardial changes, whether truly significant or not, must remain a debatable question here. Jollasse⁴⁰ recorded an unusual instance of polymyositis (no rash present) in which the postmortem examination revealed a verruca on one aortic leaflet, with obliteration of the pericardial cavity, it seems fair to note that the precise classification of the type of polymyositis in this case has been questioned, with considerable justification, by other critical observers, and the status of the entire case is best considered *sub judice*. It must be admitted, however, that extensive studies on this phase of the subject, such as were made by Libman and Sacks³⁶ and by Gross,⁴¹ are still lacking, and it seems wise to suspend judg-

39 Potain. Morve chronique de forme anormale, Bull. et mem. Soc. med. d. hôp. de Paris 12 314, 1876

40 Jollasse, O. Ueber acute primäre Polymyositis, Mitt. a. d. Hamb. Staatskrankenanst. 1 326, 1897

41 Gross (footnotes 37 and 38)

ment There is reason to believe that in rare instances rheumatic heart disease may be encountered coincidentally Marcus and Weinstein⁴² cited a number of references pertaining to cases in which the conditions were diagnosed as rheumatic fever, but a critical analysis of these as well as of a few other examples in the literature indicates clearly that the clinicopathologic criteria for the diagnosis of rheumatic heart disease were not fulfilled In 2 of the cases cited in my previous report the conditions were also diagnosed as rheumatic heart disease, but the postmortem examinations did not substantiate this diagnosis¹

(b) Myocardial Involvement In systemic lupus erythematosus the myocardium is generally spared, at least in a clinical sense Tachycardia is frequent, but it is usually not so striking as in dermatomyositis Cardiac failure is relatively uncommon and predominantly right sided, and generally finds its explanation in widespread vascular changes such as those in the pulmonary arterioles Evidence of myocardial damage is often first encountered in connection with the study of electrocardiograms, especially those taken serially, but the changes are probably nonspecific The most common alteration is low voltage in all leads, interpreted as indicating damaged cardiac muscle, changes in the other waves and, especially, occasional prolongation of the PR complex may also be observed Postmortem examination often shows involvement of the arterioles and scattered small areas of infarction that probably correspond to the points of vascular closure³⁷ It is important to stress the consistent absence of Aschoff bodies in the heart In observations made many years ago, I noted marked dilatation of the capillaries, which teemed with blood cells, it is possible that this represents a terminal phenomenon in these cases, and it may be encountered in other organs as well

In dermatomyositis symptoms and signs referable to the myocardium are more frequent than has been commonly believed Persistent tachycardia, often observed even in the afebrile periods, may be an outstanding feature, its occurrence during convalescence may be regarded as an evidence of activity in the process, despite involution in the other manifestations In other cases the patients may have palpitations, dyspnea, edema, cyanosis and pallor and perhaps arrhythmia, but it is not clear in all instances that the complaints are truly of cardiac origin, each case has to be individualized A few observers have recorded electrocardiographic evidence of myocardial damage,⁴³ but the studies on

42 Marcus, I H, and Weinstein, J Dermatomyositis Report of a Case with a Review of the Literature, *Ann Int Med* 9 406, 1935

43 Friedman, E D Dermatomyositis, *M J & Rec* 123 382, 1926 Marcus and Weinstein⁴²

this phase of the subject are still fragmentary ^{43a} In some instances there is a definite degree of congestive heart failure associated with the usual signs of this complication An occasional investigator has found slight evidence of myocardial degeneration, such as swelling and early pyknosis of the nuclei in individual fibers,⁴⁴ a mild degree of fatty degeneration¹⁸ as well as scattered areas of edema with notable dilatation of the capillaries and occasional formation of a fibrinous thrombus within these vessels These and similar changes seem not to be pathognomonic, or even highly characteristic, of dermatomyositis, and most observers have felt that these alterations are disproportionately mild when compared to the severe process in the voluntary striated muscles However, Lorenz⁴⁵ reported the occurrence of hemorrhagic areas in the myocardium of 4 patients who were afflicted with hemorrhagic polymyositis and noted a reciprocal relation between the extent and severity of the alterations in the voluntary striated muscles and those of the changes in the cardiac musculature The relation of these conditions to ordinary dermatomyositis is, however, still unsettled, but Lorenz was aware of the fact that occasionally relatively severe changes may be observed in the myocardium of patients with ordinary dermatomyositis In the cases recorded by him the supervention of this complication caused sudden death or a rapidly fatal course On the whole, then, the ordinary typical examples of dermatomyositis show no pathognomonic lesions in the heart, and only occasionally are the symptoms referable to this organ sufficiently pronounced to obscure the characteristic manifestations of this disease

(c) Pericardial Disease In systemic lupus erythematosus involvement of the pericardium may be accompanied by an audible rub, such murmurs or indistinguishable ones may also be produced sometimes by pleuropericardial disease Involvement of the pericardium is generally associated with atypical verrucous endocarditis or variants of it but this rule can be applied only in a broad manner Fairly large effusions may occur in this cavity and reveal themselves by roentgenographic and clinical examinations Finally, the changes found in the pericardium may be more chronic, presenting but one of the sites of chronic polyserositis Postmortem examination reveals often small

43a There is reason to believe that in some instances of dermatomyositis the electrocardiograms show low voltage due to increased resistance to the electric current imposed by widespread edematous infiltrations involving the muscles, subcutaneous tissues and even the cutis Consequently, such findings in the electrocardiograms do not always constitute positive proof of myocardial damage

44 Ingram, J T, and Stewart, M J Dermatomyositis and Poikiloderma, *Brit J Dermat* 46 53, 1934

45 Lorenz, H *Herzerscheinungen bei der akuten Polymyositis und deren Beziehungen für die Diagnostik der Letzteren*, *Deutsche med Wchnschr* 32 777, 1906

patches of pericarditis, fresh or old, sometimes more extensive lesions and occasionally more or less firm adhesions between the leaflets of the cavity with a corresponding degree of obliteration. The subject will be further discussed under the caption of serous membranes.

In dermatomyositis the pericardium may contain fluid of varying amounts, but this is generally uncommon and probably the result of an element of cardiac failure. It is therefore seen far less often in dermatomyositis than in systemic lupus erythematosus, and generally owes its origin to a different cause. In other words, involvement of the serous surfaces, common in systemic lupus erythematosus, is apparently not a feature in ordinary dermatomyositis. The only exception with which I am acquainted is the case of Jollasse,¹⁰ in which there was adhesive pericarditis, but, as stated before, the nature of the polymyositis in this example appears to be debatable.

(d) Cardiac Failure. As a rule, systemic lupus erythematosus is not terminated by myocardial failure, for the patient dies long before such changes become manifest. In occasional examples right-sided cardiac failure may be encountered in the course of this disease, and it is usual to observe then that the vascular pathologic alterations have shown a special predilection for the pulmonary circulation. It is, however, possible that there may be occasional exceptions to this rule.

Failure of the right side of the heart in varying degrees may be encountered proportionately more often in cases of dermatomyositis, and it is to be correlated with degenerative myocardial damage as well as with the strain placed on the heart by other complications, such as the respiratory symptoms. Involvement of the pulmonary vessels, in a manner analogous to that in cases of systemic lupus erythematosus, seems to be excessively rare. In instances of hemorrhagic polymyositis, which may possibly be regarded as a congenial of ordinary dermatomyositis, cardiac failure is generally due to involvement of the right ventricle, but occasionally the left side of the heart is also affected by extensive hemorrhage, sudden death is therefore occasionally encountered.

9 *Disease in the Serous Membranes*—Involvement of the serous membranes represents a feature of great importance in systemic lupus erythematosus. Though cardiac and renal factors may sometimes contribute to render these manifestations more prominent, disease in the serous membranes is generally primary and independent. Symptoms referable to this condition are often encountered early in the course (for example, pleural friction rub), intercurrently (for example, enlargement of the heart due to pericardial effusion) and, finally, as one of the outstanding features in the disease (polyserosal form of systemic lupus erythematosus, for example, accumulations of ascitic fluid and occasional attacks of abdominal pain). Involvement of these cavities and their coverings is generally recognizable during life, involvement

to milder degrees which gives rise to few or no symptoms may be observed post mortem (localized patches of serofibrinous or fibrous pericarditis as well as localized similar implication of the pleurae, which is common, and of the peritoneum, which is relatively uncommon)

In dermatomyositis phenomena referable to these membranes are but rarely encountered. For example, onset with pleurisy or pericarditis or with the picture of chronic polyserositis is almost unknown. Abdominal pain is generally found, on close examination, to be caused by involvement of the abdominal musculature (case 5 previously reported¹). I am excluding a few instances of dermatomyositis in which accumulations of fluid were observed in the various cavities, in these cases the clinical picture of serous involvement was not striking, and the manifestations, which were generally first discovered at necropsy, appeared to be either dependent on a degree of cardiac failure, usually of a progressive, insidious type, or secondary to some other cause, such as a pneumonic process accompanied by pleural adhesions.

In this respect, then, the clinical pictures of systemic lupus erythematosus and dermatomyositis seem to show important differences.

10 *Anomalies of the Lymph Nodes*—Systemic lupus erythematosus is often accompanied by moderate enlargement of the lymph nodes, localized (cervical, axillary) or generalized.⁴⁶ There are, however, instances in which the cervical glands become as large as a fist or even larger, persist in this form for varying periods or break down with the extrusion of necrotic, often infected, tissue. It appears that this is what used to be called "scrofulous" glands (a few cases were undoubtedly tuberculous, which is to be expected in populations heavily infected with the disease), under this term, however, many instances of nontuberculous infections of lymph nodes were often included.^{2a} The superficial lymph glands show, on microscopic examination, a nonspecific hyperplastic condition and in occasional instances areas of necrosis of nontuberculous nature. In the case reported by Ginzler and Fox⁴⁷ the prominence of the latter feature first suggested the diagnosis of tularemia.

In addition to the superficial lymph nodes, the deeper ones are also involved. Postmortem examination reveals frequently a generalized enlargement of the lymph nodes in the chest and in the abdomen, in the latter situation they may constitute a striking feature. Those in the chest (tracheobronchial chain) are sometimes complicated by tuberculous caseation in varying stages of healing, generally restricted in extent, occasionally more widespread within individual lymph nodes. It seems

46 Keil, H. (a) Tuberculous Skin Lesions, *New England J. Med.* **218** 783, 1938, (b) footnote 2b

47 Ginzler, A., and Fox, T. T. Disseminated Lupus Erythematosus in a Youth, with Some Unusual Findings, *Arch. Path.* **26** 916 (Oct.) 1938

probable that the few instances of miliary tuberculosis complicating systemic lupus erythematosus may have been caused by a lighting up of such foci, a phenomenon that probably also occurs intercurrently in the course of other diseases. The lymph nodes in the abdomen are generally succulent in appearance and moderately enlarged, on cross section they show an edematous aspect, occasionally scattered areas of necrosis of a yellowish or grayish white color and sometimes discrete foci of hemorrhage. Microscopic examination shows that these necrotic areas are generally free from the ordinary alterations seen in cases of tuberculosis, and tubercle bacilli are not revealed by the Ziehl-Neelsen stain. In previous publications⁴⁸ it was stated that the gross appearance of tuberculosis may be simulated in various lymph nodes, especially those in the abdominal cavity, yet, minute anatomic studies failed to reveal changes consistent with those of a tuberculous nature. Exceptions to this rule are relatively uncommon, and all such lymph nodes should be examined microscopically, instead of reliance being placed solely on macroscopic appearances.

In one instance, on which I have notes, the changes in the lymph nodes were regarded by the pathologist as supporting a diagnosis of reticulosis, the case having been presented as a clinical example of Still's disease or Felty's syndrome.⁴⁹ In investigating this case, the protocol of which I studied in 1930 together with some of the available material, it became apparent to me that the rash of acute lupus erythematosus and the urinary findings had not been evaluated properly, and, indeed, the kidneys were discarded. This occurred in the days before the clinicopathologic features of systemic lupus erythematosus (such as rash, renal changes clinically and at autopsy, articular manifestations and vascular lesions) were understood and before it was generally appreciated that atypical verrucous endocarditis might be absent grossly in such instances.^{36a} The occurrence of "reticulosis," a pathologic change probably nonspecific, was given undue emphasis, and it will be pointed out later that the same has been done in the rare examples of dermatomyositis in which a similar manifestation may be encountered. Here again, it is apparent that the pathologist must be prepared to correlate his observations with the clinical findings in order to avoid overstressing a nonspecific, though not common, alteration.

In cases of dermatomyositis involvement of the lymph nodes, although not infrequently observed clinically, appears to be less common than in those of systemic lupus erythematosus and rarely becomes as pronounced as in cases of the latter disease. It is probable that occasional exceptions

48 Keil (footnotes 2 and 46a)

49 Baehr, G, and Klemperer, P. Clinico-Pathologic Conference at the Mount Sinai Hospital, 1927-1928, case 295924, postmortem 6429. This case involves a typical instance of acute lupus erythematosus with clinical evidence of renal disease, presented by Baehr and Klemperer in the conference as an example of Still's disease or Felty's syndrome in an adult, the kidneys in this case were discarded.

will be found. In several instances I have observed generalized lymphadenopathy, moderate in degree. In Fiedler's patient⁵⁰ this was accompanied by some pain. In 1 instance showing features "intermediate" between systemic lupus erythematosus and dermatomyositis,³⁸ the lymph nodes, among other organs, revealed areas of nontuberculous necrosis, and similar manifestations have been recorded occasionally in the literature. There are, also, a few instances, among them the case recorded by Davison,⁵¹ in which there was an associated nonspecific hyperplastic condition of the more deeply situated lymph glands, a pathologic phenomenon of apparently banal significance.

On the whole, then, lymphadenopathy is a feature encountered more often in cases of systemic lupus erythematosus, in which it sometimes takes on a magnitude and gross appearance simulating tuberculous lymph nodes.

11 *Involvement of the Spleen*—Splenomegaly may be met with both in instances of systemic lupus erythematosus and in those of dermatomyositis, but in neither disease is it likely to attain an extreme grade. The clinical attributes are not distinctive, and the point is best remembered in a negative way, for there is the possibility of confusion with other diseases. At the postmortem examination the splenomegaly, when present, is likely to show features that differentiate these two conditions from one another.

In cases of systemic lupus erythematosus examination of the spleen may show evidence of vascular closure apparently of local origin (old and fresh infarcts, single or multiple and generally small) or of scattered areas of necrosis, these findings are rare in authentic examples of dermatomyositis. Microscopically, a variety of vascular alterations may be encountered, a description of which is not essential to this presentation. It may, however, be noted that in all probability these changes are not pathognomonic of this disease.

In cases of dermatomyositis enlargement of the spleen is usually attributed to a generalized infection. The spleen is generally firmer than it is in the ordinary acute infections, and on microscopic examination there is observed a hyperplastic pulp, with increase in its constituents and some congestion. Other investigators are of the belief that splenomegaly associated with dermatomyositis is to be regarded as spodogenous, attributable to the absorption of degenerated products in the broken-down muscles.

Here again, systemic lupus erythematosus manifests evidence of its generalization, while dermatomyositis seems to behave more like a

50 Fiedler, E. Ueber einen Fall von chronischer Polymyositis mit hochgradiger Eosinophilie und periodisch wiederkehrenden fieberhaften Exacerbationen, *Munchen med Wchnschr* **78** 1176, 1931.

51 Davison, C. Dermatomyositis. A Clinicopathologic Study, Report of a Case with Complete Necropsy, *Arch Dermat & Syph* **19** 255 (Feb) 1929.

restricted infection, with secondary effects on the spleen. A more intensive investigation of this phase of the subject would be desirable.

12 *Disease in the Liver*—Areas of necrosis, apparently similar to those occurring in the lymph nodes and in the spleen, may be seen occasionally in the liver in cases of systemic lupus erythematosus. Thus far, such an appearance has not been described in connection with authentic cases of dermatomyositis.

13 *Involvement of the Brain*—The cerebral manifestations of systemic lupus erythematosus have been but little studied. In some instances convulsions form an interesting feature in the clinical picture, and these may be encountered in the absence of a pronounced degree of azotemia. In 1 instance under my observation the spinal fluid of a patient who presented no evidence of syphilis showed a colloidal gold curve of the parietic type, this finding, though rare, seems to have some interest in view of the common observation of a positive Wassermann reaction in cases of systemic lupus erythematosus. Tremaine⁵ recorded the occurrence of adhesive meningitis in a single case, and I have observed an instance in which the postmortem examination revealed chronic meningoencephalitis. It is probable that microscopic studies, thus far few, will show vascular alterations in the capillaries and in the somewhat larger vessels. The entire subject is in want of investigation.

In typical instances of dermatomyositis the occurrence of such phenomena has not been recorded.

B LABORATORY DATA

1 *Urimalyses*—The subject of the contents of the urine has been discussed in the section devoted to renal disease. The question of porphyrinuria requires fresh and extensive investigations before the data recorded in the literature may be accurately assessed, and it will not be considered here.

2 *Blood Counts*—In association with both diseases secondary anemia of variable degree may occur. It may be absent in some cases or it may, on the other hand, attain a severe grade within a short period. When the platelet count is reduced, the hematologic formula of aplastic anemia may be simulated, but in these conditions there will be found some evidence of regeneration of the blood elements. The color index is generally below 1.

In cases of systemic lupus erythematosus leukopenia (absolute in many cases, relative in others) is so frequent an occurrence as to justify the rank of an outstanding feature of the disease. It is, however, also encountered in occasional instances of dermatomyositis, though not nearly so often. In instances of both diseases, also, the leukopenia is usually dependent on a decrease in the lymphocytes, and the polymorpho-

nuclear leukocytes generally show a shift to the left in an increase in the young forms. In cases of systemic lupus erythematosus small numbers of abnormal cells of the myelocyte series may be encountered in unusual instances. On the other hand, there are many examples of these diseases, especially systemic lupus erythematosus, in association with which relative lymphocytosis may be observed. In still other cases there may be an increase in the number of monocytes, this is especially encountered in cases of dermatomyositis, but it may also occur in occasional examples of systemic lupus erythematosus. The one apparently distinguishing feature, when it is present, is an increase in the number of eosinophils in instances of dermatomyositis. It used to be thought that muscular disease accompanied by eosinophilia invariably meant trichinosis, but this combination of phenomena may also be seen in association with dermatomyositis. It is believed by many that this feature is dependent on the reaction of the body to the rapid and widespread destruction of muscular tissue. In cases of systemic lupus erythematosus I have not yet encountered a single instance of eosinophilia, either early in the course or as a postinflammatory phenomenon in the few cases in which there is temporary recovery, for example from pneumonia. Exceptions to this rule, if they exist, are probably uncommon, and appear to concern cases illustrating a "transitional state," for instance those with features suggesting systemic lupus erythematosus associated with muscular manifestations of severe grade.

In both diseases leukocytosis occurs commonly in the presence of a complicating infection or suppurative process (such as bronchopneumonia, sinusitis and suppuration of the middle ear). This is of special interest in cases of systemic lupus erythematosus, in which the bone marrow may apparently be depressed, but it is clear that this depression is only relative and may be overcome by other factors, particularly intercurrent infections. In these diseases, but especially in dermatomyositis, this is accomplished by an increase in the polymorphonuclear leukocytes accompanied by relative or absolute lymphopenia. In case 5 of my previous report¹ the white cell count was well over 70,000 with an increase in the polymorphonuclear cells. In dermatomyositis Schuermann^{3b} has attributed the lymphopenia to the widespread shunting of lymphocytes into the muscular tissue, the site of the inflammatory reaction, but it seems likely that the bone marrow is simultaneously affected by this disease. In systemic lupus erythematosus the cause of the phenomenon is problematic at present, although one may consider the factor of involvement of the lymph nodes, commonly encountered in association with this condition. A high leukocyte count due to an absolute increase in the eosinophilic cells may be observed in occasional examples of dermatomyositis, under special circumstances the clinical picture would then simulate closely that of periarteritis nodosa.

Diminution in the number of platelets is far more commonly encountered in association with systemic lupus erythematosus, and, indeed, there are instances in which the hematologic formula of thrombopenic purpura may be simulated closely. I have recorded a group of cases in which splenectomy was successfully performed for what was supposed to be ordinary thrombopenic purpura, the apparent cure being succeeded, within eight to ten months or more, by the appearance of systemic lupus erythematosus.⁵² It is common to observe in cases of systemic lupus erythematosus marked decreases in the platelet count, with succeeding numeric fluctuations, and it is possible that these may be dependent on the inclusion of thrombocytes within "hyaline thrombi" in the capillaries and somewhat larger vessels, on the other hand, it is not possible at present to eliminate the factor of damage to the bone marrow. Less commonly a similar phenomenon may be encountered in cases of dermatomyositis in which, also, fluctuations in the number of platelets have been observed.⁵³ In both diseases purpuric lesions may occur in the skin and mucous membranes as a superimposed or independent manifestation.

3 *Metabolic Studies*—The nitrogen metabolism has been discussed briefly in the section devoted to a consideration of the renal changes. Here it remains to add several other subjects of interest.

(a) *Calcium in the Blood*—In systemic lupus erythematosus the calcium value of the blood is within the limits of normal. There are, however, occasional instances in which this value is diminished independently of renal insufficiency or of a lowered albumin content in the blood and in which there occurs deposition of calcium in the subcutaneous tissues. A few instances may show a definite, though not striking elevation in the blood calcium. The reasons for these variations are at present unclear. In dermatomyositis, also, there are variations within the normal limits and occasionally marked abnormal fluctuations in the same case. Thus, Evans⁵⁴ described an example in which the values ranged from 8.7 to 14.5 mg. Marinesco⁵⁵ observed an instance in which the blood calcium was 16.8 mg, but this is unique. Petges⁵⁶ recorded an elevation in the calcium in the blood in cases of poikilodermatomyositis associated

52 Keil, H. Relation Between "Systemic" Lupus Erythematosus and a Peculiar Form of Thrombocytopenic Purpura, *Brit J Dermat* **49** 221, 1937.

53 Marinesco, G., Draganesco, S., Facon, E., and Buttu, G. Studium eines Falles von Polymyositis haemorrhagica mit Purpura, *Deutsche Ztschr f Nervenhe* **143** 229, 1937. Schuermann^{5b}

54 Evans, P. R. Case of Dermatomyositis, *Brit J Dermat* **49** 122, 1937.

55 Marinesco, G., in Brouardel, P., and Gilbert, A. *Nouveau traité de médecine et de thérapeutique*, Paris, J. B. Baillière et Fils, 1910, vol. 38.

56 Petges, G. Notions nouvelles sur la poikilodermatomyosite et processus voisins (Poikilodermatomyosite avec concrétions calcaires), *Arch dermat-syph de l'Hôp St Louis* **5** 177, 1932.

with the deposition of calcium in the subcutaneous tissues. The significance of all these observations remains unclarified, and too much reliance should not be placed on these chemical studies as indicating an alliance between diseases such as dermatomyositis and scleroderma.

In cases of both systemic lupus erythematosus and dermatomyositis calcific deposits may occur in the subcutaneous tissues, while in rare instances of the latter disease the muscles may be similarly involved. The relation of these phenomena to the blood calcium is obscure, though it seems probable that they are unrelated in a direct sense, in any event, there is need for further investigation of the problem.

(*b*) Creatine and Creatinine Metabolism. In dermatomyositis creatine is excreted in pathologic amounts in the urine, with simultaneous diminution in the creatinine. This as well as other related phenomena appears to be dependent on the degree of muscular damage and as such is likely to be encountered in many other similar diseases, for example, trichinosis, pseudohypertrophic muscular dystrophy, myositis fibrosa and other myopathies. The subject need not be discussed further except to stress the point that such chemical disturbances merely indicate the occurrence of muscular disease and afford no clue as to the precise nature of the disease. It seems probable that similar changes will be found in the rare example of systemic lupus erythematosus accompanied by muscular atrophy, but there is need for further research to substantiate the point.

Preliminary investigations seem to indicate that lactic acid metabolism is not significantly altered in dermatomyositis, but the observations are too few as yet. In rare instances of this disease the content of uric acid in the blood has been observed to be elevated.

(*c*) Carbohydrate Metabolism. It has been observed that damaged muscles show a diminished content in glycogen, and that under such circumstances there may be an increased sugar tolerance. This phenomenon has not been studied adequately as yet in cases of dermatomyositis. It is interesting that there are on record a few examples of this disease in which the blood sugar content was much below the lower limits of normal,⁵⁷ but the significance of this finding remains to be evaluated.

(*d*) Sodium and Chloride Metabolism. As both conditions may occasionally simulate Addison's disease, it seems desirable to pursue studies relating to the metabolism of sodium, potassium and chloride. It appears, however, that a low sodium value in the blood is not pathognomonic of Addison's disease. Despite the claim of an occasional author, it can be stated confidently that neither systemic lupus erythematosus nor dermatomyositis has been shown, with reasonable certainty, to be

⁵⁷ Randolph, C. C. Calcinosis Universalis and Dermatomyositis, *J. Pediat.* 4: 342, 1934.

related in any way to Addison's disease, and the same can be said of scleroderma. Too much reliance has been placed on superficial resemblances in the clinical picture, the postmortem material has been evaluated uncritically for the most part, few thorough chemical studies have been pursued, and undue stress has been laid on therapeutic tests of doubtful import. Reinvestigation of this phase of the subject seems in order.

4 *Serologic Data*—In cases of systemic lupus erythematosus the blood often gives a positive Wassermann reaction or an anticomplementary reaction. This seems to be more than simple coincidence for the following reasons: 1 The incidence appears to be considerable, as I have encountered the phenomena in more than 10 cases of this disease and have data on several others. 2 The blood often gives an anticomplementary reaction on one or more occasions and may finally yield a positive reading. 3 With apparent improvement or temporary cure of an attack of the condition, the serologic reaction of the blood to the Wassermann test may become negative, under such circumstances a negative reaction may be regarded as a good prognostic sign, though there is, to be sure, great variability in the results of this test. When the Wassermann reaction is positive, the results range between 1 and 3 plus, rarely to 4 plus, and it is the rule to encounter wide fluctuations in successive reactions. Moreover, it is also relatively common to observe variations depending on the particular serologic technic employed, for example, the Wassermann test may be negative while the Kahn is weakly positive and vice versa. Many years ago Gennerich suggested that the positive Wassermann reaction obtained in cases of lupus erythematosus was caused by a lymphocytic "ferment" derived from enlarged lymph nodes observed commonly in this disease. The present knowledge would lead the investigator to expect that the factor responsible for these abnormalities would be found in the globulin fraction in the blood. Recently Coburn and Pauli,^{57a} studying 2 classic examples of systemic lupus erythematosus with anticomplementary blood and increased globulin values in the serum, observed that the factor responsible for the anticomplementary reaction was in the globulin fraction, this observation seems significant as a preliminary step in the elucidation of the nature of the phenomenon. An occasional observer has also noted an increase in the globulin value in the serum,⁵⁸ and I have made the same observation in a few cases. There are, however, many instances of systemic lupus erythematosus in which this seems to be absent, and, contrariwise, there is no precise correlation between the serologic phenomena mentioned and the globulin values in the serum.

^{57a} Coburn, A. F., and Gutman, A. B. Personal communications to the author.

⁵⁸ Taussig, A. E. Still's Disease with Hyperglobulinemia, *J. Lab. & Clin. Med.* **23** 833, 1938. Coburn and Gutman ^{57a}

Not rarely in such cases of systemic lupus erythematosus treatment with antisyphilitic drugs has been employed, the results of such therapy being indifferent or even harmful. Furthermore I have observed an unusual instance of the disease, in which tests of the spinal fluid of a girl who also had atrophy of the optic nerve⁵⁹ resulted in a verified dementia paralytica type of colloidal gold curve, a single determination for globulin gave a moderately positive result. Neither in this case nor in the others with positive serologic reactions of the blood could syphilis be established as a cause. That syphilis may occur coincidentally in patients with systemic lupus erythematosus is to be expected in occasional instances, on the other hand, there are instances of true syphilitic eruptions on the face, especially those with unilateral distribution, in which the "superficial" variants of lupus erythematosus may be strikingly simulated, and these cases often defy the diagnostic acumen of the most expert. Finally, I have notes on 1 example of systemic lupus erythematosus in which the blood of the patient agglutinated itself spontaneously while the Wassermann reaction of the blood was 3 plus, in addition, a blood count revealed a fair number of myelocytes, so that leukemia was suspected. It follows, then, that each case must be individualized, with the understanding that a positive Wassermann reaction may sometimes complicate the clinical picture of systemic lupus erythematosus.

In cases of dermatomyositis the incidence of positive Wassermann reactions⁶⁰ seems to be small, and I have not met with any case illustrating this association. There are a few recorded examples of dermatomyositis in which syphilis was invoked as a cause⁶¹. Perusal of the protocols on these cases reveals that the diagnosis was based on doubtful clinical criteria in the era before the Wassermann test or on therapeutic tests that gave dubious results. In view of the rarity of such instances (nearly all were cases of polymyositis without cutaneous lesions), the spontaneous recoveries of persons with this disease and the possibility of a coincidental syphilitic infection, it seems fair to conclude that there are few, if any, cases of dermatomyositis in which syphilis has been definitely proved to be the cause.

59 Goldstein and Wexler²⁷ Records of the Mount Sinai Hospital²⁸

60 Schwarz, R. Beitrag zur Aetiologie der Polymyositis, Frankfurt Ztschr f Path **25** 141, 1921. Milian, G. Erythroedeme myasthenique, Rev franç de dermat et de vénerol **10** 347, 1934.

61 Herrick, J. B. Polymyositis Acuta, with Report of a Case Presumably of Syphilitic Origin (Myositis Syphilitica), Am J M Sc **111** 414, 1896. Lorenz, H. Die Muskelerkrankungen, Vienna, A. Holder, 1898, p. 227. Hoffmann, V. Syphilis der Muskeln, in Jadassohn, J. Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1928, vol. 17, pt. 3, p. 241.

C PROGNOSIS

The prognosis for recovery, complete or incomplete, is grave in almost all authentic instances of systemic lupus erythematosus in which the patients have been followed for more than five years. The so-called cures that have been recorded concerned patients who experienced temporary improvement and were not observed long enough to warrant a precise opinion. It must, however, be admitted that this phase of the subject has not yet been thoroughly enough exploited to permit drawing of absolute conclusions. Thus, I have encountered cases in which the clinical course, which was finally fatal, ran far beyond the five year period from onset of constitutional symptoms referable to this disease⁵². It is not uncommon to encounter patients who show cutaneous lesions year after year, especially during the summer months, and in these patients the condition may go on for a long time before manifesting evidence of systemic involvement. Early in my observations I regarded evidence of renal involvement as indicating a fatal prognosis in the immediate attack of the disease, but this rule, while nearly always true, appears to have exceptions. Thus, I have several times observed more or less transient recoveries, at least in a clinical sense, of patients who manifested undoubted signs of disease in the kidneys, nevertheless, continued observation taught that these recoveries were only temporary. It is curious that in a few of these cases examination of the fundi showed swelling of the regions of the papillas, as described in a previous section in this paper. No conclusions can, however, be drawn from this combination of events, as occasional patients may, in the absence of such changes, experience sufficient improvement to permit the term "temporary recovery" to be applied to their condition. The reversal from a positive to a negative serologic reaction of the blood is interpreted in the same way as the aforementioned data.

On the other hand, I have pointed out in other publications that the temporary absence of detectable systemic manifestations indicates a good prognosis only in the immediate attack, for this may be followed, after variable periods, by a fresh exacerbation with lethal outcome. I have notes on 1 case in which the patient had discoid atrophic lupus erythematosus for about twelve years before exposure to ultraviolet rays caused generalization of the disease, postmortem examination revealed the typical findings of systemic lupus erythematosus. Such instances would lead one to believe that the disease may occasionally occur in a more benign form and that there may be patients, especially those seen in early stages before the supervention of constitutional symptoms, in whom the disease may either run a prolonged course or who may even recover completely. It is apparent that the subject is best studied by one who has access to material in a dermatologic dispensary and medical

wards. It is for this reason that I believe the last word on prognosis has not yet been spoken, though for the vast majority of patients showing evidence of systemic reaction death seems to be practically invariable. The causes of death in instances of this disease are numerous. Summarized briefly, they are (1) bronchopneumonia arising from a superimposed infection, the swallowing of debris by patients with oral, pharyngeal or tracheal lesions and occasionally secondary infection of small infarctions in the lungs (closure of pulmonary vessels), (2) renal insufficiency, (3) a state of profound "toxemia" in which either the vascular lesions to be discussed later are relatively insignificant or absent, or the extent of pneumonic disease is apparently too slight to explain the death satisfactorily, (4) intercurrent bacteremia due to (a) the common aerobic bacteria, such as *Streptococcus haemolyticus* and *Staphylococcus aureus* and (b) tuberculous bacillemia with miliary tuberculosis, (5) cardiac failure, especially affecting the right side, (6) meningeal disease, and (7) combinations of the foregoing factors, etc.

The prognosis for dermatomyositis seems to be much better than for systemic lupus erythematosus, though it is still serious, as a mortality rate of over 50 per cent has been recorded^{6b}. It must be stressed, however, that this is probably a conservative estimate, for in many instances dermatomyositis, like systemic lupus erythematosus, has shown itself to be a relapsing and recurrent disease. Nevertheless, there are cases in which the condition appears to enter a chronic phase or in which complete recovery apparently supervenes or in which the clinical picture is sooner or later succeeded by that of myositis fibrosa with its crippling effects. Thus, Weber and Gray observed a patient who remained cured for at least thirteen years. Weinberger⁶² recorded an instance in which there was freedom from disease for nine years, followed by an attack that proved fatal. In Turner's third case^{3a} the patient had the disease at the age of 5 years, with complete recovery, after a symptom-free interval of eight years there was a much severer recurrence which apparently entered a chronic phase of the disease. Blau¹² recorded an instance in which the first attack at the age of 14 years was interpreted as poliomyelitis, six years later there was a recurrence, and the clinical picture of myositis fibrosa was now well established. There are many other examples in which the patient was known to have had the disease for a decade or more, and it suffices for the present to take cognizance of the point. Throughout this presentation it has been noted that the clinical picture of the disease may begin with what seems to be systemic lupus erythematosus and that after a variable interval there appear the characteristic features of dermatomyositis. The cases of the myasthenic

62 Weinberger, M. Ueber ein chronisch verlaufende Polymyositis mit Ausgang in progressive Muskelatrophie, *Wien med Wchnschr* 83 100, 1933

form of lupus erythematosus (Gougerot) and of myasthenic erythredema (Milian), in some of which there was apparent cure, represent in all likelihood instances of ordinary dermatomyositis, the reasons for this view will become clear on consideration of the cutaneous manifestations and the clinical features of these conditions as well as a number of other syndromes, the names of many of which have now entered the phase of patronymic nomenclature

The causes of death in cases of dermatomyositis are somewhat different from those in instances of systemic lupus erythematosus. Briefly summarized, they are (1) bronchopneumonia chiefly due to paralysis of the small muscles in the pharynx, the intercostal muscles or the muscles in the diaphragm, as a consequence of which aspiration of material, infected or noninfected, is likely to occur (involvement of these small muscles is not necessarily accompanied by death, for in occasional instances temporary or more permanent recovery may take place, nevertheless, evidence of such paralysis is to be regarded apprehensively), (2) intercurrent complications, such as the invasion of the blood stream by *Str. haemolyticus* from a sacral decubitus sore, (3) cardiac failure, generally affecting the right side but occasionally affecting the left side as well, and (4) unexplained causes, such as "cachexia." Sudden death from suffocation is commonly encountered in patients with dermatomyositis as a result of marked involvement of the small muscles already mentioned, but this type of outcome is not rarely met with in patients afflicted with systemic lupus erythematosus, in most instances of the latter disease the cause seems obscure

D PATHOLOGIC DATA CRITICAL ANALYSIS OF THE "VASCULAR CONCEPT" OF SYSTEMIC LUPUS ERYTHEMATOSUS AND DERMATOMYOSITIS

The data recorded thus far indicate that systemic lupus erythematosus and dermatomyositis, while often affecting the skin in somewhat similar fashion, display a predilection for certain parts of the body in a manner peculiar to themselves. Thus, in systemic lupus erythematosus the kidneys, heart, articulations and serous membranes are especially involved, in dermatomyositis, the muscular system. From time to time observers have hazarded the opinion that these organs are implicated chiefly through their respective blood supply and have accordingly grouped these as well as other conditions under the generic head of "diffuse vascular disease." Thus, in cases of systemic lupus erythematosus the major alterations may be observed in the small blood vessels, usually the capillaries, although the arterioles and venules, occasionally even the larger vessels, may also be affected. In cases of dermatomyositis the vascular changes, when encountered, seem to concern arterioles

somewhat larger (muscles), though usually smaller than those affected in periarteritis nodosa, while the capillaries (skin, muscle) are also commonly involved. If the unique case recorded by Talbott and his associates⁶³ is accepted as one of dermatomyositis, this instance would be, so far as I can ascertain, the only one in which the interlobular arteries in the kidneys were so strikingly affected. In view of the rarity of such alterations in dermatomyositis, it would seem wise to place this case to one side until the precise nature of this instance as well as that of the anatomic findings is fully established. In the discussion to follow I am less concerned with the histologic descriptions of the pathologic alterations than with the interpretations and conclusions drawn from them.

There is, in my opinion, little justification for classifying these diseases as genuine examples of "diffuse vascular disease," except occasionally, for this designation carries with it at least two important implications. 1 It presupposes that the vascular changes are universal, easily recognized and fairly constant, it is my belief that this is actually not the case. 2 It allows for confusion with other conditions in which the vascular tree also apparently bears the brunt of the process, so far as pathologic examinations are concerned, to mention only a few, arteriosclerosis (arteriolosclerosis), periarteritis nodosa and typhus fever⁶⁴. Indeed, there is reason to believe that the vascular alterations observed in cases of systemic lupus erythematosus and dermatomyositis explain the clinical features far less satisfactorily than, for example, in cases of periarteritis nodosa. The term "diffuse vascular disease," while therefore possessing some utility, has little diagnostic value per se, its use is the equivalent of saying that a patient has purpura, without attempting a finer clinical differentiation. A similar criticism applies to the use of the term "mesenchymal disease," which represents only an expedient way of expressing an anatomic concept. But the problem does not end with the qualification of these terms, for soon several disturbing questions arise.

63 Talbott and others²². Footnote 23

64 Baehr, G, and Sacks, B. The Occurrence of Glomerulonephritis in Association with Verrucous Endocarditis, *Proc New York Path Soc* 23: 64, 1923. This is an example of how far astray the concept of "diffuse vascular disease" ("endotheliotropic virus") may lead. This term is applied not only to ordinary glomerulonephritis, but also to 3 cases that are now believed to be examples of rheumatic fever. In the same communication, reference is also made in a similar sense to 2 instances of atypical verrucous endocarditis, the 3 aforementioned cases were detailed by Dr. E. Libman in a letter written to Dr. L. Gross, chairman of the Laboratory Committee of the Mount Sinai Hospital, dated Feb. 10, 1936, and Dr. L. Gross, in a personal communication, stated that these cases were definite examples of rheumatic fever to be reported again by him in detail at some future time. The vascular lesions described in this paper were originally found by B. Sacks (E. Libman. Letter written to Dr. L. Gross, chairman of the Laboratory Committee of the Mount Sinai Hospital, dated Feb. 10, 1936).

1 *Systemic Lupus Erythematosus*—A Can one speak of lesions pathognomonic of this disease? It is my belief that, on the whole, this question may be answered in the negative. The “wire-loop” lesions occurring in the glomeruli of the kidneys in cases of systemic lupus erythematosus may be regarded as highly characteristic. Interestingly enough, I have encountered them in a case of this disease accompanied by marked wasting of muscles in the limbs and other parts. In another publication^{2b} I have briefly discussed the importance of these alterations in the kidneys and there expressed the view that the “vascular concept” does not explain every phase in the disease process in systemic lupus erythematosus. The “wire-loop” lesions may be regarded as a secondary expression of a disease the cause or causes of which still remain to be determined, though certain precipitating factors are known, for example, sunlight. The evidence compiled thus far appears to indicate that these changes are “toxic,” occurring in patients with an unstable vascular system. Beyond this view, which is of course restricted in its scope, it seems unwise to go at present. Yet, despite these limitations, the vascular lesions in the kidneys have had, and still enjoy, a definite importance for 1. They are often the earmark of systemic lupus erythematosus, and fewer cases of this sort would have been overlooked or remained buried in the records had the possible significance of these alterations been appreciated, for example, prior to 1930,⁴⁹ for it was by the correlation of these vascular lesions (originally as “hyaline thrombi”) with the dermatologic and internal medical aspects that I was enabled in 1930 to arrive at a unified clinicopathologic conception of systemic lupus erythematosus.⁶⁵ 2. Their occurrence permits the pathologist to ally, at least temporarily, certain obscure conditions that at present defy precise classification. In doing this, the pathologist must not forget the clinical aspects, for such lesions or similar ones may be encountered in association with various other diseases, such as eclampsia, mycosis fungoides, “hyperergic inflammation” and probably other conditions. A concept based alone or chiefly on the renal lesions, without regard to the remainder of the clinical picture, would be one sided. Thus, in the days before the clinical features of systemic lupus erythematosus were sufficiently appreciated, the lesions in the kidneys, especially those accompanied by some degree of focal necrosis or marked hyalinization, were regarded as allied to the somewhat similar findings associated with subacute bacterial endocarditis or even healed subacute bacterial endo-

⁶⁵ Keil, H. Communication to the Libman Fellowship Foundation, Feb 5, 1931. Libman, E. Personal communication to the author, Nov 22, 1931, personal communication to Dr L. Gross, Chairman of the Laboratory Committee of the Mount Sinai Hospital, Feb 10, 1936. Gross, L. Personal communication to the author, Sept 4, 1937.

carditis On the basis of resemblances in appearance, which may be considerable, it was concluded that the lesions in cases of systemic lupus erythematosus are embolic While this may possibly be true in the case of subacute bacterial endocarditis, there is adequate evidence that appears to contradict the application of such a belief to systemic lupus erythematosus

Similarly, the vascular lesions reported as occurring in the heart and other structures in systemic lupus erythematosus are probably not pathognomonic of this disease, for similar or even identical changes may be encountered in occasional examples of rheumatic fever⁶⁴ and other conditions The perivascular fibrosis observed sometimes in the spleen is probably also not a specific finding

B Are the vascular lesions always present in cases of systemic lupus erythematosus? It seems probable that such alterations are found in a large percentage of typical instances of systemic lupus erythematosus, but there are cases in which assiduous examination of the kidneys, for example, may fail to reveal these changes or in which their intensity and distribution hardly parallel the severity of the clinical features In other words, there is great variability in the degree of severity and distribution of the lesions not only in the kidneys but also in other parts of the body, including the skin, the vascular alterations considered to be characteristic may be insignificant in extent and distribution, minimal or even altogether wanting Mallory,⁶⁶ who has made a thorough study of the pathologic picture of this disease, concluded that there is no constant type of vascular lesion, and, moreover, he was able to find the "wire-loop" lesions in only one-half the cases or less

Does the absence of "hyaline thrombi" in the skin mean that the condition under consideration is not systemic lupus erythematosus? An occasional case has been reported in the literature as showing this change,⁵ and I can substantiate this point on the basis of 2 additional instances These findings are, however, uncommon, and I have several times seen fragmented edematous collagenous bundles confused with them, moreover, study of serial sections and prolonged search are often essential to the discovery of them It is probable, therefore, that too much reliance should not be placed on alterations of this sort, which, moreover, probably occur in other diseases as well The pathologic diagnosis of systemic lupus erythematosus may be suggested by biopsies of skin on the basis of certain combinations of changes that will not be discussed here That analogous alterations may often be seen in cases of dermatomyositis is not surprising when one considers the similarities

⁶⁶ Disseminated Lupus Erythematosus, Cabot Case 24201, *New England J Med* **218** 838, 1938, Acute Disseminated Lupus Erythematosus, Cabot Case 24341, *ibid* **219** 273, 1938

in the structure of the eruptions. In any event, it seems doubtful whether one can speak of pathognomonic changes in the blood vessels as observed in these cases.

Of what importance is it to realize the limitations in such studies? There are instances in which, on the basis of similarities in vascular lesions, an alliance between diseases has been or will be advocated. Thus, Volk's⁶⁷ case has been cited in several reports as an example of periarthritis nodosa occurring in association with systemic lupus erythematosus, yet critical examination of the data reveals that the clinical features were entirely consistent with the diagnosis of systemic lupus erythematosus, while the criteria for the diagnosis of periarthritis nodosa were doubtfully fulfilled. Likewise, the occasional observation of certain types of vascular changes in the vessels of the kidneys in patients with scleroderma, for example, does not warrant, on this basis alone, an alliance between this disease, systemic lupus erythematosus, periarthritis nodosa, dermatomyositis and other such conditions. Here again, the clinical features and the collateral factors must be considered closely. The concept of "hyperergic inflammation" rests on similar grounds, and one has but to read the various reports concerned with this pathologic phenomenon to realize the disparity in diseases assembled under this head. The observation of "reticulosis" in a lymph node in a person with systemic lupus erythematosus was once made the basis of a theory on Still's disease or Felty's syndrome, and an interesting phenomenon, hardly pathognomonic per se, constituted the cornerstone for the interpretation of a case that presented the typical clinical features of systemic lupus erythematosus.⁴⁹

Friedberg, Gross and Wallach⁷ contributed an outstanding study on what they called nonbacterial thrombotic endocarditis, differentiating it from other varieties of endocarditis, especially atypical verrucous endocarditis and rheumatic heart disease. It appears, however, that nonbacterial thrombotic endocarditis may occur in association with many other pathologic conditions as well as superimposed on other types of endocardial disease. Beyond the observation that such verrucae may be confused with those observed in other conditions, it seems difficult to see how this finding could be used as a means of differentiating diseases, its very universality would seem to militate against such a view. Furthermore, it is my belief that the occurrence of nonbacterial thrombotic endocarditis would not eliminate the diagnosis of systemic lupus erythematosus, even if it were not superimposed on the more characteristic atypical verrucous endocarditis. In any event, knowledge of this type of endocarditis, the pathogenesis of which is still obscure,

⁶⁷ Volk, R. Periarthritis nodosa bei einem Lupus erythematoses chronica cum Exacerbatione, *Dermat Ztschr* **53** 682, 1928.

is important, if only to help one avoid confusing it with other diseases, for example, rheumatic fever and subacute bacterial endocarditis

C Another disturbing question relates to instances in which the post-mortem examination fails to reveal the changes regarded as characteristic of systemic lupus erythematosus. Does the absence of such alterations eliminate this diagnosis? It is my belief that there are occasional cases in which the clinical features are clearcut, yet in which the anatomic changes to be expected are lacking or hardly adequate to explain the entire clinical course. For example, I have observed an instance of this disease in which apparently nothing significant was observed at autopsy, except subacute pneumonia, it seems hardly likely that this finding, which was indeed the chief cause of death, could explain adequately the occurrence of a widespread eruption, accompanied by articular pains and a clinical picture that lasted several months. Again, the case recorded by Goldstein and Wexler²⁷ is another in point. Here the only pathologic alteration of note was observed in the eyes post mortem, and it seems hardly likely that this could explain the rapidly fatal course and the degree of "toxemia" shown by the patient. It is for this reason, among others, that the primary nature of the vascular lesions seems doubtful. It must therefore be concluded that there are examples of this disease in which the clinical aspects apparently assume greater diagnostic importance than the pathologic findings and in some instances may even override positive changes of more or less doubtful significance. These data are therefore in agreement with the views propounded by Dr. Soma Weiss.⁶⁶

2 *Dermatomyositis*—In cases of dermatomyositis pronounced vascular alterations seem to be less commonly encountered, and some observers have therefore suggested that this disease be classified under two heads: (a) conditions showing changes in the blood vessels, and (b) those free from such alterations. When present, the vascular lesions apparently possess a significance somewhat similar to that in cases of systemic lupus erythematosus. In agreement with the clinical features, the pathologic changes are found chiefly in the muscular tissues. Many disturbing questions arise in the study of these cases.¹

A Are these vascular lesions, when present, pathognomonic of dermatomyositis? Two types of changes in the blood vessels have been considered as especially significant: 1. Capillary dilatation in which these vessels teem with blood elements. This appearance has been stressed by some as the primary change in the disease, and for these observers the term *angiomyositis* seems to express best the fundamental nature of this condition. Whether this appearance is indeed representative of the initial disturbances in this disease has not yet been definitely determined, but it seems fair to note that such changes may be

encountered as a banal pathologic phenomenon in other conditions as well and are therefore difficult to assess. 2 Various other types of vascular damage. Changes ranging from subintimal involvement with its secondary effects to a true "necrotizing arteriolitis," in which the brunt of the process is apparently borne by the media or other portions of the vascular parietes, have been recorded as occurring in cases of dermatomyositis. Fahr has attempted to ally these changes with those seen in association with periarteritis nodosa, using the latter term in its broadest pathologic connotation. It is my belief that, while there may be similarities in the pathogenesis of such vascular alterations, nothing more than this can be concluded. With a few exceptions, it can be said that knowledge of the clinical picture is essential before claims can be made for the specificity of such vascular lesions.

B Are these vascular changes always found in typical cases of dermatomyositis? There are many examples of this disease in which the extent of the damage to the blood vessels seems relatively insignificant in comparison with the degree of muscular involvement. It must be admitted, however, that this observation cannot be judged rigorously in the absence of serial sections of muscle or an examination of large portions of it, for it is conceivable that significant vascular lesions may be overlooked owing to insufficient search. Yet even thorough post-mortem studies indicate clearly that in many instances the muscular changes appear to be disproportionately severe as compared with those seen in the blood vessels, and there are examples of this disease in which the latter alterations seem altogether insignificant or completely absent. For these reasons some investigators believe that the same etiologic agent may attack both the muscles and the blood vessels either concurrently or independently, and for many of these observers it seems more likely that the muscles are primarily affected.

It becomes evident, then, that the nature of the muscular alterations, whether primarily, secondarily or concurrently involved, whether degenerative or inflammatory, still admits of considerable debate. Further, the degenerative changes in the muscles appear to be even less specific than the vascular changes described, and, indeed, the whole subject of the pathologic anatomy of the myopathies is in want of fresh investigation. In the average case of dermatomyositis examination of muscular tissue generally reveals widespread alterations in the parenchyma, these being easily recognized. Yet numerous reports on other diseases, for example, scleroderma, show that simple atrophy, atrophy from disuse, atrophy from mechanical pressure and other types of atrophy have been regarded as identical with the changes occurring in dermatomyositis. What makes the problem especially difficult is the observation that the alterations in the muscles may be considerably influenced by all sorts of secondary phenomena, and this occurs not only

in dermatomyositis but in many other diseases as well. It seems that here again there must be a close clinicopathologic correlation until such time as better criteria are evolved. As long ago as 1888 Jacoby,¹³ in comparing the muscular alterations in his case of polymyositis with those associated with typhoid fever, remarked that even if the results of microscopic examination were identical, "we could not be justified in considering the processes as clinically analogous." The difficulties in evaluating the nature of muscular pathologic changes become manifest on study of the excellent monograph written by von Meyenberg.⁶⁸ It is probable that the muscles are more often affected in a wide variety of diseases than is generally suspected, and it is essential to examine this tissue under manifold conditions. These alterations need to be studied in relation to the clinical features, and perhaps then more information will be forthcoming in regard to the nature of these changes, the most favorable sites for removing specimens for biopsy and the diagnostic value of such examinations and other matters. The occasional observation of "reticulosis" and of a chronic granulomatous change about blood vessels are interesting findings to which, however, undue etiologic significance must not be too readily attached. It is my belief that at the present time the clinical aspects are of greater importance in the classification of examples of this disease, but in all instances a clinicopathologic correlation seems not only desirable but also essential.

In the discussion of these diseases only brief mention has been made of a number of phenomena which appear to be of "vasomotor" origin and for which it seems unlikely that there will be found anatomic changes sufficiently marked to characterize these symptoms. These manifestations (for example, the pronounced sweating occasionally associated with dermatomyositis) seem to require physiologic studies for clarification.

SUMMARY

This study is concerned with a comparative analysis of the essential clinicopathologic features presented by systemic lupus erythematosus and dermatomyositis. Among the clinical phenomena encountered in both diseases are fever, pains generally regarded as articular, similar cutaneous and oral lesions, sensitivity to sunlight, Raynaud-like symptoms, lymphadenopathy, splenomegaly, leukopenia, tendency to purpura, alopecia of the scalp, sterile cultures of blood, muscular involvement and renal disease. At times both diseases may also run an afebrile course, and the clinical picture may occasionally be dominated by what may be called the sequelae of these conditions. Despite these

⁶⁸ von Meyenberg, H. Die quergestreifte Muskulatur, in Henke, F., and Lubarsch, O. *Handbuch der speziellen pathologischen Anatomie und Histologie*, Berlin, Julius Springer, 1929, vol. 9, pt. 1, p. 299.

similarities and the occasional overlapping of features, the average typical example of each disease runs a fairly distinctive course. The main body of the paper is devoted to an analysis of the differences in the clinico-pathologic attributes. These are studied under the following headings: (1) age, sex and seasonal incidence, (2) cutaneous lesions, (3) disease in the muscles, (4) involvement of subcutaneous tissue, (5) articular involvement, (6) renal disease, (7) ophthalmoscopic observations, (8) cardiac involvement, (9) disease in the serous membranes, (10) anomalies of the lymph nodes, (11) involvement of the spleen, (12) disease in the liver and (13) involvement of the brain. Certain laboratory data are also compared. Likewise, differences in the prognosis are briefly discussed. Finally, the pathologic data thus far available are subjected to a critical examination with respect to their significance for diagnosis, and an effort is made to expose some of the many problems encountered in the evaluating of such observations.

ARTERITIS OF THE TEMPORAL VESSELS

REPORT OF A CASE

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During the past few years an occasional case has been observed of an inflammatory condition selectively involving the temporal arteries which differs clinically and pathologically from the conditions classed under the headings of thromboangitis obliterans, periarteritis nodosa and rheumatic arteritis. Biopsy shows that the attack of the invasive agent is centered on the medial coat, producing moderate necrosis with hemorrhage at times, and that destroyed areas are replaced with granulation tissue in which numerous giant cells are invariably present. All coats may be involved, which results in intimal thickening and round cell infiltration of the adventitia, and the process may extend to tissues around the arteries. The lumen of the vessel may be closed by thrombosis. Formation of small aneurysmal sacs arising in the media is not observed in this disease as it is in periarteritis nodosa.

The cause of this clinical syndrome is unknown, and for want of better nomenclature it is called merely arteritis of the temporal vessels. Cultures of material from the media of a number of resected temporal arteries, blood cultures, agglutination tests for typhoid, paratyphoid, undulant fever and tularemia, examination of the spinal fluid, inoculation of animals and the use of special staining methods for microorganisms of syphilis and tuberculosis have failed to yield definite information of the specific causative agents. Roentgen examination of the head, thorax and spinal column, as well as urinalysis, has given essentially negative results.

The disease affects both sexes and occurs usually in persons past 60 years of age, often in persons with signs of arterial hypertension and arteriosclerosis. The illness lasts about five or six months, with some tendency to relapse but with eventual complete subsidence. It is well known for its nonfatal outcome in contrast to periarteritis nodosa, which generally produces fatal results within a year. The entity is characterized by periarteritis and arteritis of the temporal vessels. Other vessels have been thought to be involved, such as the cerebral,

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retinal and radial arteries In the case to be reported here it was rather obvious clinically that the occipital arteries were inflamed at the same time

The most outstanding complaint has been that of dull, throbbing headache which is usually worse at night Also, there appear fever, night sweats, poor appetite, loss of weight and strength, anemia, weakness and mild leukocytosis, these symptoms may precede by several weeks the signs of inflammatory involvement of the temporal arteries In time the vessels become enlarged and tortuous and are surrounded by areas of hyperemia Small nodules may be seen or felt over the main branches or the smaller ones, and pulsations may be only partly absent or entirely absent, according to the patency or the degree of occlusion of the lumen

The condition was first recognized as a distinct arterial entity at the Mayo Clinic in the spring of 1931, approximately eight years before the reading of this paper The observers, Horton, Magath and Brown, published a report of 2 cases, in the winter of 1932¹ and the spring of 1934² MacDonald and Moser³ reported a similar case in the spring of 1937, Horton and Magath⁴ reported a total of 7 cases (observed at the Mayo Clinic) in the fall of 1937 and mentioned a complete report of another case which they had received from three physicians in Uruguay One year prior to the time of this report, two physicians of London, England, Jennings⁵ and Bain,⁶ published their findings in 3 cases Recently Horton stated in a personal communication to me that he had observed 3 additional cases in the past six months The following case was first recognized by me as one in which the signs and symptoms of arteritis of the temporal vessels were apparent seventeen months ago It is the sixteenth case of this condition to be placed on record

REPORT OF CASE

History of Illness—A married white woman aged 65 years was seen in my office Sept 18, 1937 She was a former music teacher whose husband was unemployed She was neurotic and hypertensive She had been referred to me

1 Horton, B T, Magath, T B, and Brown, B E An Undescribed Form of Arteritis of the Temporal Vessels, Proc Staff Meet, Mayo Clin **7** 700-701 (Dec 7) 1932

2 Horton, B T, Magath, T B, and Brown, B E Arteritis of the Temporal Vessels A Previously Undescribed Form, Arch Int Med **53** 400-409 (March) 1934

3 MacDonald, J A, and Moser, R H Periarteritis and Arteritis of the Temporal Vessels A Case Report, Ann Int Med **10** 1721-1726 (May) 1937

4 Horton, B T, and Magath, T B Arteritis of the Temporal Vessels Report of Seven Cases, Proc Staff Meet, Mayo Clin **12** 548-553 (Sept 1) 1937

5 Jennings, G H Arteritis of the Temporal Vessels, Lancet **1** 424-428 (Feb 19) 1938

6 Bain, C W C Arteritis of the Temporal Arteries, Lancet **1** 517 (Feb 26) 1938

by a general practitioner, who considered her completely invalidized by pains about the head which she had had for eleven weeks. These were thought to be due to arterial hypertension and known to have been present for ten years. They were ascribed to exhaustion brought on by the unwelcomed presence of a relative in the household.

The pains in the head had been constant, dull and throbbing, usually disturbing the patient's sleep at night. For the first five weeks they were limited to the occipital region, but in the past six weeks they had been present in the temples. They were not associated with effort or posture. They had been so severe as to cause almost complete loss of willingness to eat, and her nourishment for some time had consisted of two slices of bread a day, which had resulted in a loss of 15 pounds (6.8 Kg) in weight. The tongue had been red and burning, and she had noticed swelling in the region of the salivary glands. She felt faint, weak and at times feverish. She was admitted to the hospital on September 20.

Personal History—The patient's father and mother died in old age. A brother died at 50 years of age of a general physical breakdown, and a sister succumbed to carcinoma at 55 years of age. The patient's husband, a jeweler, had been unemployed for many years. Her two children were instructors in the field of art.

The patient had suffered intensely from dysmenorrhea and migraine in youth and had been traumatized during parturition. At the age of 43 years a right nephropexy, an appendectomy, a partial oophorectomy and suspension of the uterus had been performed. These operations had been followed shortly by removal of a tumor from the right cheek and removal of a urethral caruncle. The menopause had taken place at the age of 50, without untoward symptoms.

Two years before she was seen by me, the patient had been examined by an internist, who recorded a blood pressure of 234 systolic and 112 diastolic. He found the peripheral arteries generally thick walled and tortuous and could find no pulsation in the left dorsalis pedis artery. There was severe trichophytosis on the toes of the left foot. A toe nail was removed, and the patient was advised as to the care of chronic nervous exhaustion and constipation, for which she had previously interviewed several physicians. One month later she wrote that she was no better, was tender in most parts of her body and ached from the waistline down.

Physical Examination—The patient was intelligent. She showed some dehydration, emaciation and pallor. She was nervous and tense. Immediately before her admission to the hospital her blood pressure was 160 systolic and 110 diastolic. With rest in bed and the use of sodium phenobarbital it rapidly declined to as low as 120 systolic and 70 diastolic and remained within normal range in the two determinations made daily. The temperature varied from 97 to 101.4 F and the pulse rate from 76 to 92 per minute, the respiratory rate was stationary at 20 per minute.

Both anterior branches of the temporal arteries, but especially the left, were prominent from a point just above the temporomandibular joint for a distance of about 7 cm. They were somewhat thickened and tortuous, of irregular caliber and without pulsation throughout, but they were not nodular. The tissue around the central portion of the left vessel was hyperemic, and the preauricular glands were moderately enlarged. On questioning, the patient always designated the region of these arteries as the site of her pain of the past few weeks, especially at night. At various times they were exquisitely tender, and after biopsy material had been taken the swollen and reddened proximal end of the left vessel was especially tender.

The pain had been located formerly in the occipital arteries and was excruciating. Later there was pain in the anterior branches of the temporal arteries, and, although pain had largely disappeared from the former site, the occipital arteries were still tender, tubular and thick walled. Their caliber was regular, and no nodules were present, nor could any satellite glands be palpated. These arteries were likewise involved in an inflammatory process for a distance of about 7 cm from a point above their emergence into the occipital triangle. No other peripheral vessels were similarly involved.

The extraocular movements of the eyes were normal. The pupils were small but reacted normally to light and accommodation. The media were clear, and the retinal arterioles showed sclerotic changes, but neither hemorrhage in the fundi nor papilledema was present. The nasal spaces and mucous membranes were normal, and there was no evidence of infection of the paranasal sinuses to inspection or transillumination. The ears were normal. The tongue was bluish scarlet, with atrophy of the marginal papillae. The tonsils were atrophic and without infection. The pharynx, nasopharynx and larynx were normal. The patient was endentulous.

The neck was normal. The breasts were normal. The heart was not grossly enlarged, and there was slight accentuation of the aortic second sound. The lungs were normal. The liver and spleen were not palpable, and no mass was felt in the abdomen. Vaginal and rectal examinations revealed no abnormality. The reflexes were intact and normal throughout. Pulsations in the dorsalis pedis and posterior tibial arteries on the right were only moderate, on the left they were absent.

Laboratory Observations—The urine showed a trace of albumin. The concentration of hemoglobin was 80 per cent (Dare). The red blood cells numbered 4,070,000 and the white blood cells 12,450 per cubic millimeter, with neutrophils 89 per cent and lymphocytes 11 per cent. The Wassermann reaction of the blood serum was negative. The sedimentation rate of the red blood cells was 28 mm in a sixty minute period (Wintrobe). The bleeding and clotting times and the platelet count were normal. Agglutination tests for undulant, typhoid and paratyphoid A and B fevers gave negative results. The value for urea nitrogen was 18 mg, that for creatinine 18 mg, that for nonprotein nitrogen 54 mg and that for sugar 111 mg per hundred cubic centimeters of blood. The carbon dioxide-combining power was 52 volumes per cent. Analysis of the gastric contents showed a value for total acidity of 38 and for free hydrochloric acid of 16, in terms of cubic centimeters of one-tenth normal sodium hydroxide.

Roentgen and Electrocardiographic Studies—Roentgenograms of the paranasal sinuses were normal. A roentgenogram of the chest showed mild left ventricular hypertrophy, aortic dilation and tortuosity and mild fibrosis throughout both lung fields. Fluoroscopic and roentgen examination of the gastrointestinal tract after a barium meal revealed no abnormality. An electrocardiogram revealed a heart rate of 80 per minute, sinus arrhythmia, left axis deviation and mild myocardial damage.

Treatment—The patient's total stay in the hospital amounted to four weeks. The first week was devoted to combating dehydration and undernourishment, to relief of pain and to a search for the cause of her profound discomfort. It was difficult for the patient to lay her head on a pillow on account of tenderness over the occiput, the pain in the temples was excruciating. She insisted that her suffering was not due to elevated blood pressure, renal disease, infection of the paranasal sinuses or gastrointestinal disturbances.

Potassium iodide and dicalcium phosphate were administered orally, concentrated liver extract and vitamin B₁ parenterally and sodium iodide, sodium salicylate and iron cacodylate intravenously. These gave little or no relief. The patient received some comfort from the frequent use of codeine sulfate and sodium phenobarbital administered hypodermically. Nourishing fluids were given intravenously, and eventually the caloric intake became satisfactory.

Because of fever, leukocytosis and designation of the anterior branch of the left temporal artery as the site of greatest discomfort, a diagnosis of subacute arteritis was made after one week in the hospital, and a segment of the vessel was removed for cultural purposes and for examination.

Biopsy and Pathologic Report—With the region under local anesthesia an incision was made over the middle portion of the anterior branch of the left temporal artery, and a segment of the vessel, measuring about 2 cm, was removed (fig 1). A culture was made of material from the tissue. Grossly, the tubular



Fig 1—Site of removal of the biopsy specimen. A small segment was taken from the anterior branch of the left temporal artery. Note that the artery is thickened and tortuous, with an irregular caliber.

piece of tissue was 1.5 cm in length and 0.3 cm in diameter. Microscopically, sections of the artery revealed variable degrees of chronic inflammation (figs 2 and 3), and the intimal lining was extremely thinned. There was an organized thrombus which occluded the lumen except for a narrow crescentic channel. In the media there was marked infiltration of mononuclear cells, with frequent neutrophils and an appreciable number of eosinophilic polymorphonuclear cells. Granulation tissue was present throughout. The adventitia was only mildly involved in the inflammatory process. The diagnosis was chronic arteritis. Cultures made on blood agar plates from the specimen removed from the temporal artery yielded a growth of gram-positive cocci in clusters.

Subsequent Course—The area around the distal end of the severed artery became hyperemic and tender. However, the patient in a short time commented on her delight in the relief from severe pain at the site of removal of the biopsy specimen, presumably this relief was due to interruption of the pain pathway of

the sympathetic nervous system. During the remainder of her sojourn in the hospital the patient continued to improve. The temperature gradually subsided, until in three weeks it was nearly normal. She was able to rest and sleep better. Her intake of food soon amounted to 2,000 calories per day. Peculiarly enough, the presence of residual pain was noticeably affected by the intramuscular administration of vitamin B₁. The daily supply of this vitamin in amounts ranging from 500 to 2,000 international units afforded marked relief, and trial withdrawals repeatedly permitted the return of the pain within twelve to sixteen hours.

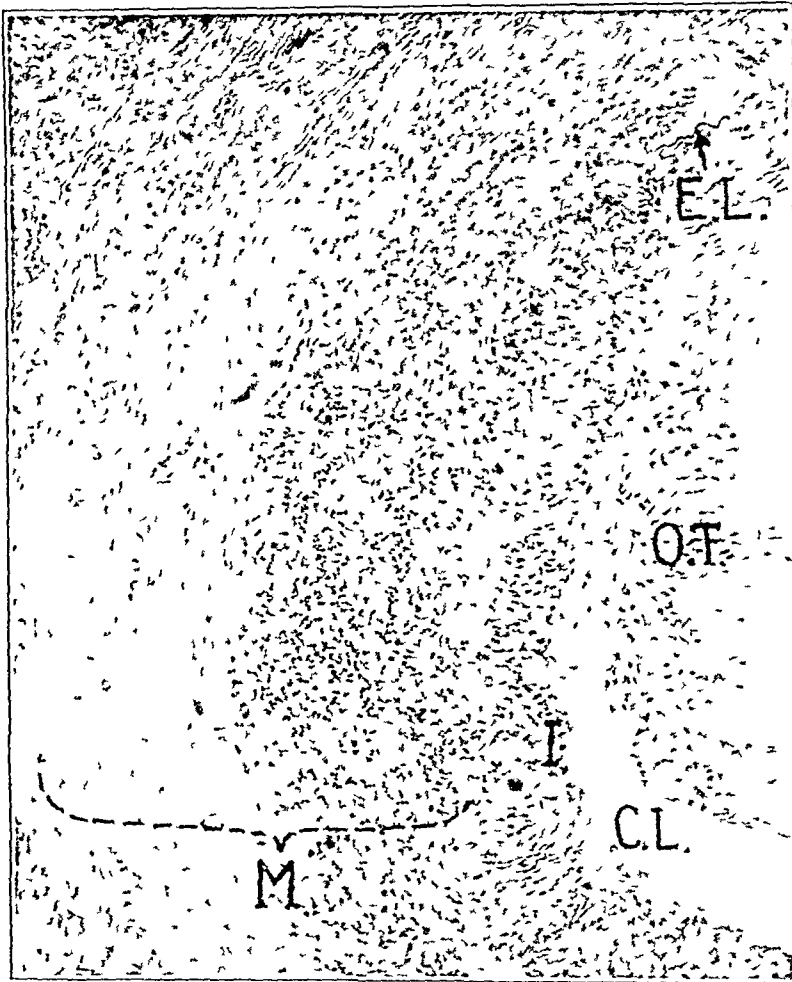


Fig 2—Low power photomicrograph of a cross section of the temporal artery *M*, the media, showing a vast amount of cellular infiltration, necrosis and granulation tissue. *E L*, the internal elastic membrane. *I*, the intima, somewhat thinned. *O T*, an organized thrombus. *C L*, the crescentic lumen.

Follow-up—The patient left the hospital October 17, and during the next six weeks she was seen several times. She remained constantly in bed for the first two weeks, this was followed by graduated intervals of sitting in a chair and of walking short distances. Her temperature declined to a normal level, her intake of food remained reasonably good. On November 17 her blood pressure was 138 systolic and 94 diastolic, and she had a feeling of slight increase in strength. Vitamin B₁ had been injected intramuscularly twice a week. Parenteral administration of tissue extract and oral administration of iron were ordered.

The incision over the left superficial temporal artery healed quickly, and there was rapid subsidence of signs and symptoms of inflammation in both superficial temporal arteries. The left occipital artery was normal to palpation and gave no distress, but the right one was occasionally causing a dull ache, especially at night, and was still thick walled and tender. However, in two weeks these symptoms responded to palliative and supportive treatment.

On Jan 19, 1938, after prolonged worry over financial affairs, she noticed a return of cardiorenal symptoms on a hypertensive basis. Her blood pressure was 220 systolic and 110 diastolic. However, she was entirely free from pain over

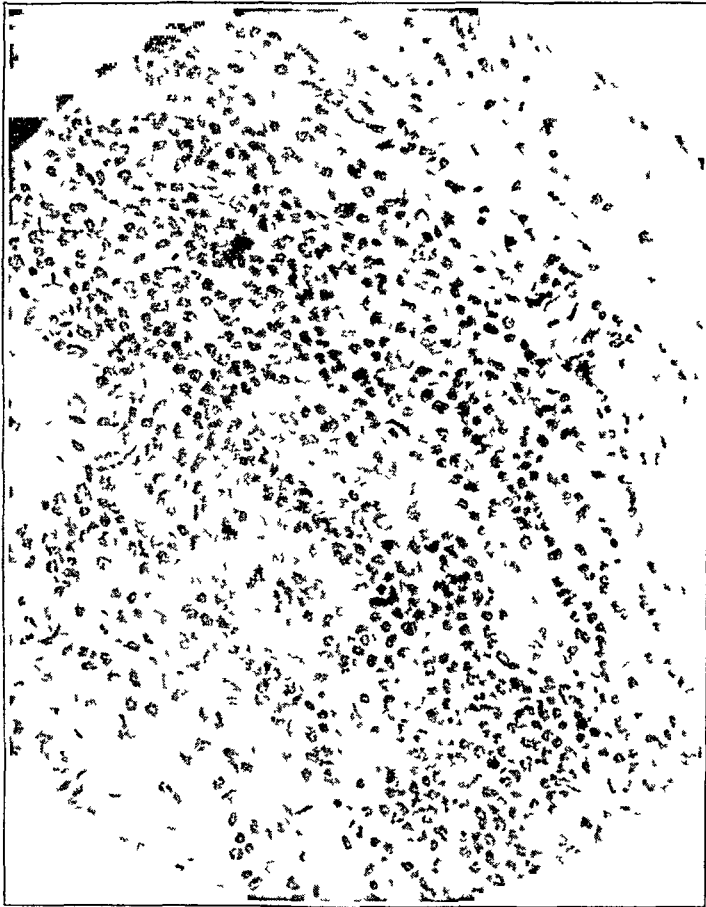


Fig 3—High power photomicrograph of a cross section of the media of the temporal artery. There is evidence of marked infiltration with neutrophilic and eosinophilic polymorphonuclear and mononuclear cells and granulation tissue.

the courses of the temporal and occipital arteries. Sedatives were supplied, but six weeks later the condition was about the same and the blood pressure still markedly elevated. During the latter part of April she felt much more comfortable, and there was considerable lessening of the hyperpiesis.

Then, one year after the patient was first seen by me (September 1938), she appeared in my office, hardly able to walk or talk because of profound weakness. The mouth was dry and the tongue red and coated, the abdomen was distended with gas, and the extremities were cold. The pulse rate was 92 per minute, and the blood pressure was 230 systolic and 120 diastolic. She admitted that she had eaten little food and had worried a great deal for several weeks. Three days

later she was readmitted to the hospital on account of vomiting and exhaustion. She sank slowly into a fairly deep coma which lasted five days. The muscles of the extremities were somewhat spastic, and she was restless in bed even though she was unconscious. The urinary bladder and the rectum were incontinent, eventually it was necessary to empty the bladder by catheter. There was no inequality or unusual change in the reflexes of the extremities. The pupils were normal in size. Fever was absent. When the pulse became feeble it was necessary to digitalize the patient. No localized inflammation of the peripheral arteries was obvious. On admission the blood pressure was 230 systolic and 120 diastolic, but under the influence of barbiturates it rapidly dropped to a normal level.

Urinalysis gave essentially negative results. The initial blood count showed mild leukocytosis and eosinophilia. Hypochloremia was present until sodium chloride was supplied by infusion. The alkaline reserve and the concentration of blood urea nitrogen were normal. Examination of the spinal fluid was not performed. The value for "fasting blood sugar" was 183 mg per hundred cubic centimeters, but with the daily administration of 15 units of protamine zinc insulin hypodermically it became normal. Dextrose in saline solution was given intravenously, and eventually 100 Gm of carbohydrate was fed orally each day. Finally, after the evidence of disturbance of the carbohydrate mechanism had disappeared, the insulin was discontinued and the patient was placed on a general diet.

The patient rallied from her extreme weakness, with definite and fairly rapid improvement in color, hydration, weight and strength. She suffered from vertigo for several weeks, and an otologist concluded that the hyperirritability of the labyrinths was on an arteriosclerotic basis. An oculist reported moderate sclerotic changes in the retinal arterioles. Recovery was satisfactory enough within six weeks to permit the patient to leave the hospital. Again she remained in bed, most of the time at home, for a long period. Even though her blood pressure had risen to its previous high levels, she showed many signs of improvement in health, which was partly due to her attempt to suppress worry and to partake of a better diet.

Comment—My final opinion as to the cause of the coma was that it might have been a cerebral vascular mishap, the exact mechanism of which, however, was not apparent to me. Obviously, whatever took place was a complication or a sequela of arterial hypertension and arteriosclerosis, just as the previous occurrence of inflammation of the temporal arteries probably can be considered an aftermath of the same conditions. The same form of arteritis that afflicted the temporal vessels may have involved the cerebral vessels.

There is presumably no specific treatment for the disease. In this case, before a biopsy specimen was taken, narcotics and sedatives were frequently employed to give relief from pain. Administering vitamin B₁ parentally and sodium iodide, sodium salicylate and iron cacodylate intravenously had little or no effect. The patient noticed immediate comfort after removal of a moderate-sized segment of the inflamed artery, which was maintained by injection of considerable amounts of vitamin B₁ until healing took place.

SUMMARY

A case of inflammation of the temporal arteries is presented. For a considerable period before diagnosis the associated headache was attributed to severe arterial hypertension. Undoubtedly, the occipital arteries were involved in a similar inflammatory process at the same time. Nine months after the subsidence of signs and symptoms, the patient suffered a cerebral vascular mishap, which probably was due to arteritis of the cerebral vessels, of the same nature. Interruption of the pain pathway of the sympathetic nervous system after resection of an arterial segment and injection of vitamin B₁ produced relief from pain. Many points in favor of designation of this condition as a separate entity of arteritis, especially of its distinction from periarteritis nodosa, may be found in the reports of the 16 cases now on record.

BODY BUILD AND HYPERTENSION

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Thus far there has been no conclusive proof in the medical literature that there is a correlation between body build and blood pressure. There are many authors who have stated with considerable positiveness that there is no relation. Bauer¹ and Braun² observed no characteristic build among hypertensive persons, and Hay³ stated that both thin persons and those of the sthenic habitus are susceptible to hypertension. Alvarez and Stanley⁴ stated "There is no correlation with height or with the degree of stockiness or ranginess. Contrary, then, to the general impression, thick-set, stocky men are apparently no more likely to develop hypertension than are their tall, thin, asthenic-looking brethren."

Those who have contended that there is a correlation between body build and blood pressure have arrived at their conclusions through an impression of total weight rather than through one of the size of the skeletal frame, and generally without sufficient anthropometric and statistical support. Von Bernuth⁵ observed "The view held hitherto was simply supported by inspection and intuitive processes, which do

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1 Bauer, J. *Die konstitutionelle Disposition zu inneren Krankheiten*, Berlin, Julius Springer, 1924

2 Braun, L. *Constitution and the Circulatory System*, *Wien klin Wchnschr* **43** 142, 1930

3 Hay, J. *The Significance of a Raised Blood Pressure*, *Brit M J* **2** 43, 1931

4 Alvarez, W. C., and Stanley, L. L. *Blood Pressure in Six Thousand Prisoners and Four Hundred Prison Guards. Statistical Analysis*, *Arch Int Med* **46** 17 (July) 1930

5 von Bernuth, F. *Constitution (Review of Literature)*, *Monatschr f Kinderh* **71** 165 (Nov) 1937

not suffice. Exact measurements are necessary." Von Beinuth's observation is pointedly illustrated by the commonly accepted belief that flat-chested persons are more prone to tuberculosis—an opinion apparently the result of purely intuitive processes. Weisman's⁶ recent monograph showed that the normal chest is flat and that the chest of the tuberculous patient is relatively deep.

A serious criticism of most of the existing studies on body build and blood pressure is that the series covered have been relatively small. Furthermore, in some studies the indexes of build that have been used do not adequately delineate types of build. In spite of this lack of rigidly controlled statistical studies, the prevailing opinion among medical writers is that there is a constitutional factor in the hypertensive diseases.⁷

Since there is no unanimity of opinion on the relation between gross body structure and blood pressure, any study clarifying this problem is of greatest importance. Backer^{7a} stated

If a relationship between bodily habitus and blood pressure were now clearly established, both factors, the habitus as well as its corresponding arterial tension, would most likely have to be traced to a much deeper underlying *common cause* possibly appearing early in the course of ontogenetic events.

The morphologic structure is only one manifestation of the constitutional type of the person. The total constitution, that is, the constitution considered from the psychologic, immunologic, endocrinologic and other points of view, carries with it the susceptibilities to, and the potentialities of, disease. This paper deals only with the susceptibility to hypertension as associated with the gross body build aspect of constitution. Hurst⁸ pointed out "A better knowledge of constitution should make it possible to prevent some diseases [and] to recognize others in an earlier stage than is at present possible." The recognition of a relation of a type of body build to hypertension should make possible

6 Weisman, S. A. *Your Chest Should Be Flat. The Deep Chest Makes Better Soil for Tuberculosis*, Philadelphia, J. B. Lippincott Company, 1938.

7 (a) Backer, M. *Essential Hypertension. Constitutional Considerations*, *Am J M Sc* **192** 395, 1936. (b) Palmer, R. S. *Etiologic Factors in Hypertension*, *New England J Med* **205** 233, 1931. (c) Zipperlen, V. R. *Constitutional Investigations Among Hypertensives*, *Ztschr f Konstitutionslehre* **16** 93, 1931. (d) Barach, J. H. *Constitutional Factors in Hypertensive Disease*, *J A M A* **91** 1511 (Nov 17) 1928. (e) Fishberg, A. M. *Hypertension and Nephritis*, ed 2, Philadelphia, Lea & Febiger, 1931. (f) Friedlander, A. *Hypotension*, *Medicine* **6** 147, 1927. (g) Larimore, J. W. *A Study of Blood Pressure in Relation to Types of Bodily Habitus*, *Arch Int Med* **31** 567 (April) 1923.

8 Hurst, A. F. *The Constitutional Factor in Disease*, *Brit M J* **1** 823, 1927.

the administration of preventive measures against this disease that now seems to be recognized as incurable. Huist⁸ further stated

It would seem obvious that in the practice of medicine the man is as worthy of study as the malady with which he is afflicted. But during the last twenty-five years the great advances in knowledge which have followed the application of bacteriological, biochemical, and physical methods to the investigation of disease have led to the comparative neglect of the constitutional factor.

Before proceeding with this investigation of the relation of blood pressure to body build, it was necessary to find a simple method of grouping persons according to specific types of body build. The methods commonly used by anthropometrists and the European theorists on constitution were found to be, for the most part, too complex for practical clinical research. As Graves⁹ has long pointed out, the necessary quantitative technics are merely means toward the discovering of qualitative differences. The goal is a constitutional theory that will aid clinical practice.

The first task in such a study of build as this would be to arrive at an index that would accurately delineate the two main types of body build, namely, (1) the thin, narrow-chested type, often designated as the long and thin one, and (2) the broad-chested, solid, stocky type. These opposing types merge into an intermediate one. Two extremes of build were recognized by the earliest medical writers. Hippocrates pointed out this gross division of the human race and established the two classes of build: *habitus apoplectic* and *habitus phthisic*. Gildea, Kahn and Mann¹⁰ pointed out that "two large main groups stand out. These may be roughly denoted as the stocky in build at one pole as contrasted with the thin at the other." Similarly, Stockard¹¹ concluded "The two groups into which almost all ordinary persons fall more or less exactly, may, therefore, be termed the *Linear Type* and the *Lateral Type*." It is a common practice among lay persons and professional men alike to designate the two obvious builds as either slender or broad. Terms like *asthenic*, *hyposthenic*, *leptosomic*, *dolichomorphic*, *microsplanchnic* and *cerebral* all refer to the linear type, while *sthenic*, *hypersthenic*, *pyknic*, *brachymorphic*, *macrosplanchnic* and *digestive* designate the broad, or lateral, type. For clinical practice, the importance of having a simple index for build, by means of which a quick estimate can be made of the person's gross type, cannot be overestimated.

9 Graves, W. W. Personal communication to the authors.

10 Gildea, E. F., Kahn, E., and Mann, E. B. The Relationship Between Body Build and Serum Lipoids and a Discussion of These Qualities as Pyknicophilic and Leptophilic Factors in the Structure of the Personality, *Am J Psychiat* 92:1247, 1935.

11 Stockard, C. R. Human Types and Growth Reactions, *Am J Anat* 31:261, 1923.

Such an index of build would have to take into account the person's height as well as his width. As Davenport¹² observed, a simple relation of breadth to height gives an excellent evaluation of a person's build. Most of the indexes used rely on these two basic measurements. The question of measuring the stature is a simple one, but the problem of arriving at the breadth introduces a few complications. To ascertain the breadth one might measure the intertrochanteric distance, or the intercrystal width,¹³ or the width, depth or circumference of the chest. The intertrochanteric or any hip measurement, however, introduces too large a sex variable. Moreover, it does not necessarily measure thoracic width or bulk. Davenport¹² stated

When I look at a man, or a photograph of one and think "He is slender," it is because I make a mental comparison of his breadth (of shoulders or chest) with his height and find that his breadth in comparison with that of most men I know of that height is small, or if he is stout the diameter of the chest is large in relation to stature.

The thorax is, of course, the largest body surface or bulk that can be contrasted with height. Chest width and chest circumference stand out, then, as the two most desirable measures of breadth. Since Davenport¹² has pointed out that "chest circumference bears a nearly constant relation to chest diameter," it does not matter which of these measures is used. However, circumference is probably a slightly more accurate gage of total thoracic bulk, for diameter alone excludes the varying chest depth, circumference includes both width and depth.

In this study the circumference of the chest was divided by the height to produce a ratio similar to those of Brugsch,¹⁴ Berliner¹⁵ and Livi¹⁶ and to the formula of the Marburg School¹⁷ involving thoracic circum-

12 Davenport, C. B. *Body-Build and Its Inheritance*, Washington, D. C., Carnegie Institution of Washington, 1923.

13 Lucas, W. P., and Pryor, H. B. *Physical Measurements and Physiologic Processes in Young Children. Some Correlations*, J. A. M. A. **97** 1127 (Oct. 17) 1931.

14 Brugsch, cited by Viola, G., and Benedetti, P. *Standardization of Anthropometric Measurements*, Endocr. pat. costit. **10** 446, 1935.

15 Berliner, M. *Height and Breadth Development*, Ztschr. f. klin. Med. **108** 378, 1928.

16 Livi, cited by Graffi, E. *Body Proportions and Somatic Characteristics of a Group of Girl Students at the University of Bologna*, Endocr. pat. costit. **5** 392, 1930.

17 Data concerning this formula are cited by V. Wigert (*Attempts at Anthropometric Determinations of Body Structure Types*, Ztschr. f. d. ges. Neurol. u. Psychiat. **143** 651, 1933).

It has been pointed out by some authors that this chest/height index should be modified by squaring the height or using the square root of the chest. The only

ference and body length. This index can be determined from measurements quickly made in routine examinations and accurately delineates the classic types of build. At the same time the simplicity of the chest/height index makes it useful for statistical manipulation. Without rigidly controlled statistics on a large series one can hardly show a correlation between two variables like build and hypertension. Since this study aimed at a measure of skeletal configuration, it must be noted that the weight factor was ignored entirely. Nevertheless a variable amount of obesity was included in the measurement of the chest circumference.¹⁸

STATISTICAL ANALYSIS

To ascertain the correlation of body build and blood pressure, an unselected series of records containing the results of a complete physical examination conducted by the Life Extension Examiners in the Chicago office was analyzed. From each record an abstract was made of the height, weight, blood pressure, pulse rate and chest and girth measurements. The examination was well standardized, since the same six physicians made all of the examinations, and in many cases check-up readings among the various examiners were obtained. The chest measurement was taken with a steel tape just above the nipple line during quiet breathing, in the measuring of women the tape was placed higher to avoid the inclusion of excess mammary tissue. Height was

rationale for this modification is that the chest is a two dimensional measurement whereas height is one dimensional. Actually, it makes no difference how these figures are manipulated, since the coefficients of correlation of systolic pressure to various modifications of the index remain practically unchanged. For example, the coefficients of correlation obtained for our subjects were as follows:

Correlation	1861 Men	1797 Women
C/H to systolic pressure	$= 0.184 \pm 0.022$	$\text{and } 0.299 \pm 0.022$
C/H ² to systolic pressure	$= 0.188 \pm 0.022$	$\text{and } 0.266 \pm 0.022$
C/H ³ to systolic pressure	$= 0.157 \pm 0.023$	$\text{and } 0.235 \pm 0.022$
$\sqrt{C/H}$ to systolic pressure	$= 0.184 \pm 0.022$	$\text{and } 0.280 \pm 0.022$
$\sqrt[3]{C/H}$ to systolic pressure	$= 0.153 \pm 0.023$	$\text{and } 0.234 \pm 0.022$

With the formula $\sigma_D = \sqrt{\frac{\sigma_1^2 + \sigma_2^2 - 2r_{12}\sigma_1\sigma_2}{\theta_1\theta_2}}$, the difference between any two of these coefficients would have to be at least 0.062 in order to be significant. Since the actual difference does not exceed 0.035 in any combination in the men and is only 0.065 between C/H and $\sqrt[3]{C/H}$ in the women, the modifications can add little to the value of the index. The C/H measure is used in this paper because it is the simplest and easiest to understand.

18 It is possible for a person of any build to be either underweight, medium weight or overweight, further, the person of linear or slender build, as well as the one of lateral build, may be either short or tall. These phases of the problem dealing with the interplay of obesity, height and build in their relations to hypertension have been dealt with in an article entitled "Hypertension, Obesity and Body Build" in the American Journal of Medical Science (199:819, 1940) and one entitled "Hypertension in Relation to Height. Its Variation with Body Build and Obesity" in a forthcoming issue of the Journal of Laboratory and Clinical Medicine.

measured on a specially designed apparatus in which the heels of the subject were placed against a backboard of a platform and the shoulders thrown back against a rod, the head was tilted and the subject asked to stretch to obtain the maximum height to $\frac{1}{10}$ inch (0.25 cm). The group was composed of 3,658 persons—1,861 were of the male and 1,797 of the female sex.

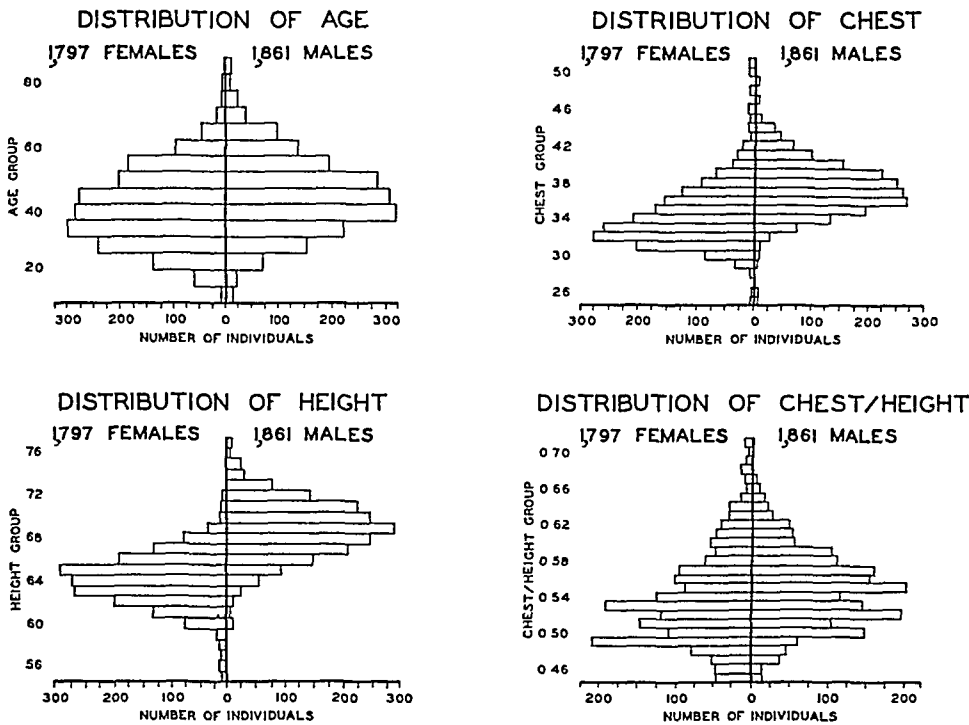


Fig 1—Charts illustrating the distribution of the physical measurements used in the study of body build and blood pressure. The statistical constants for these distributions are as follows:

	Age		Chest Circumference		Height		Chest/Height Ratio	
	Men	Women	Men	Women	Men	Women	Men	Women
Mean	43.0 \pm 0.28	38.3 \pm 0.27	37.0 \pm 0.07	33.7 \pm 0.07	68.3 \pm 0.07	63.6 \pm 0.06	0.543 \pm 0.001	0.532 \pm 0.001
Median	42.3	37.6	36.8	33.2	68.4	63.6	0.543	0.524
Mode	40.9	36.2	36.4	33.2	68.6	63.6	0.543	0.508
Standard deviation	11.9	11.4	2.83	3.16	2.8	2.5	0.044	0.052
Standard range	31.55	27.50	34.40	30.36	65.71	61.66	0.50-0.59	0.48-0.58

Distribution of Ages—Figure 1 shows that the ages of men were concentrated in the standard range¹⁹ of 31 to 55 years. The ages of the women were concentrated between 27 to 50 years. The subjects were, therefore, essentially a middle-aged group at that period when clinical hypertension is most likely to make its early appearance.

¹⁹ A standard range is defined here as the range of one standard deviation on either side of the mean, roughly rounded out to the nearest whole number. For all practical purposes, if the curve is only moderately skew, this range includes a little more than two thirds of the group.

Distribution of Circumferences of Chest—The chest circumferences of the men ranged from 24 to 47 inches (60.96 to 119.38 cm) with a concentration in a standard range of about 34 to 40 inches (86.36 to 101.60 cm). There was a slight increase in chest circumference up to about 40 years of age. The younger men (ages 20 to 30) had a chest circumference of about 34 inches (86.36 cm). At 40 years and later the most usual chest measurement was 37 inches (93.98 cm). The chest circumferences of the women ranged from 23 to 50 inches (58.42 to 127 cm), with a standard range of from 30 to 36 inches (76.20 to 91.44 cm). As with the male group, there was a slight increase with age in the chest circumference of the women.

Distribution According to Height—The average height of the men was $68\frac{3}{10}$ inches (173.48 cm), with a standard range of 65 to 71 inches (165.10 to 180.34 cm). This average is only a few tenths of an inch lower than that observed in most other studies on the distribution of height.²⁰ The average height of the women was $63\frac{6}{10}$ inches (161.54 cm), with a standard range of from 61 to 66 inches (154.94 to 167.64 cm).

Distribution of Systolic Blood Pressures—The distribution of systolic pressures is shown in table 1 to follow closely that of our larger series of 15,000 persons.²¹ The average systolic pressure for the male group was 120 mm, though the mode was lower at 110 mm. The standard range showed that for the most part the pressures of the men ranged from 102 to 139 mm. Those for the female groups averaged 116 mm, with a mode of 112 mm. The standard range of pressure among the women was from 96 to 136 mm. Low pressures occurred more frequently among the women and higher pressures slightly less frequently. However, it is important to remember that the female group was a younger group than the male group and that young women have lower pressures than do young men, while older women show pressures slightly higher than those of older men.

Distribution of Diastolic Blood Pressures—The diastolic pressures (table 1) for the men averaged 74.4 mm, with a modal pressure of 71.1

20 (a) Jackson, C. M. The Physique of Male Students at the University of Minnesota. A Study in Constitutional Anatomy and Physiology, *Am J Anat* **40** 59, 1927. (b) Jackson, C. M. Physical Measurements of the Female Students at the University of Minnesota, with Special Reference to Body Build and Vital Capacity, *Am J Phys Anthropol* **12** 363, 1929. (c) Medico-Actuarial Investigation. Statistics of Height and Weight of Insured Persons, New York, Association of Life Insurance Medical Directors and the Actuarial Society of America, 1912. (d) Ireland, M. W. The Medical Department of the United States Army in the World War, Washington, Government Printing Office, 1921, vol. 15, pt. 1.

21 Robinson, S. C., and Brucer, M. H. The Range of Normal Blood Pressure, *Arch Int Med* **64** 409 (Sept.) 1939.

TABLE 1—*Relation of Chest/Height Ratio To Blood Pressures*

	Linear Build with Chest/Height Ratios of		Intermediate Build with Chest/Height Ratios of			Lateral Build with Chest/Height Ratios of		Chest/ Height Ratios of All Types	Correlation Data	
	0.47 and Under	0.48 to 0.49	0.50 to 0.52	0.53 to 0.55	0.56 to 0.58	0.59 to 0.61	0.62 and Over			
Systolic pressure 1,861 men	45 110 to 120 mm 23 120 to 140 mm 5 140 mm and over 113 Number of subjects	74 54 63 7 198	127 147 149 30 453	112 150 157 51 470	77 117 123 57 374	26 39 76 23 164	10 19 37 23 89	171 566 628 196 1,861	Mean Standard deviation Skewness Coefficient variation Coefficient correction Test lin	0.532±0.001 0.052 0.462 9.77 r=0.194±0.022 η=0.253 ξ=0.030±0.008
Mean pressure Median pressure Modal pressure Percentage under 110 mm Percentage 140 mm and over	114 113 110 40 4	115 113 110 37 4	117 115 112 28 7	120 117 111 24 11	123 119 116 21 15	123 122 119 16 14	130 126 118 11 26	120 117 110 25 10		
Systolic pressure 1,797 women	122 110 to 120 mm 70 120 to 140 mm 28 140 mm and over 5 140 mm and over 225 Number of subjects	174 84 60 8 326	206 121 101 29 457	120 82 82 33 317	67 50 65 26 208	29 38 41 36 144	34 19 34 35 120	752 464 170 1,797	Mean Standard deviation Skewness Coefficient variation Coefficient correction Test lin	0.543±0.001 0.044 8.10 r=0.299±0.022 η=0.309 ξ=0.006±0.003
Mean pressure Median pressure Modal pressure Percentage under 110 mm Percentage 140 mm and over	109 109 108 54 2	110 109 105 53 3	114 111 107 45 6	115 114 112 38 10	120 116 112 32 13	128 120 115 20 25	129 123 110 28 28	116 112 112 42 10		
Under 70 mm pressure 70 to 79 mm 80 to 89 mm 90 mm and over Number of subjects	55 45 10 3 113	77 86 33 2 198	163 198 66 26 453	135 192 111 32 470	78 102 99 35 374	31 56 60 17 164	14 33 26 16 89	553 772 405 131 1,861	Mean Standard deviation Skewness Coefficient variation Coefficient correction Test lin	0.543±0.001 0.044 8.10 r=0.249±0.022 η=0.263 ξ=0.007±0.004
Mean pressure Median pressure Modal pressure Percentage under 70 mm Percentage 90 mm and over	71 70 70 49 3	71 72 73 39 1	73 72 71 36 6	75 73 71 29 7	75 75 71 21 9	77 79 82 19 10	79 79 77 16 18	74 73 71 30 7		
Under 70 mm pressure 70 to 79 mm 80 to 89 mm 90 mm and over Number of subjects	135 69 16 5 225	203 96 23 4 356	239 187 38 23 457	138 106 52 21 317	72 72 46 18 208	41 46 36 21 144	43 25 31 21 120	871 571 242 113 1,797	Mean Standard deviation Skewness Coefficient variation Coefficient correction Test lin	0.532±0.001 0.052 0.462 9.77 r=0.279±0.002 η=0.312 ξ=0.019±0.006
Mean pressure Median pressure Modal pressure Percentage under 70 mm Percentage 90 mm and over	67 65 61 60 2	67 66 64 62 1	69 69 69 52 5	71 71 71 44 7	74 73 72 35 9	76 75 71 29 15	77 76 74 36 18	70 70 70 49 6		

mm The standard range was from 64 to 85 mm As in the case of systolic pressure, the average diastolic pressure for the women was lower, 70.4 mm, with a mode of 70.1 mm The standard range was from 59 to 82 mm The female group showed a greater frequency of low pressures and a smaller one of high pressures than did the male group This difference is due to the high incidence of the lower pressures among younger women At the older ages the distribution of diastolic pressures among the female group was similar to that among the male group

Distribution of the Chest/Height Ratio—The index obtained by dividing the chest circumference by the height was used in this study to differentiate the broad type of build from the narrow one The simplicity of this index is its main asset Further, it is to be noted that the measure of weight is not used at all to arrive at this index Roughly, the index can be sketched easily by the rule-of-thumb statement that the chest circumference should be one-half the height, in other words, that the chest/height ratio should be 0.50 For the purpose of comparing type characteristics, three classes of persons were established on the basis of the following types of build (1) a linear type, with a chest/height ratio of less than 0.50 (chest measurement less than one-half the height), (2) an intermediate type of build, with a ratio within the standard range of 0.50 to 0.59, and (3) a lateral type, with an index of 0.59 or over (chest circumference very large in relation to height) This is a purely arbitrary division and is used only for the purpose of comparing extremes Throughout this study finer subdivisions in type of build are usually given which merge from one type into the other

The mode of the chest/height distribution was 0.54 for the men with a standard range of from 0.50 to 0.59 As would be expected, the women showed a narrower type of build The average chest/height ratio for women was 0.53 with a mode slightly less than 0.51, a standard deviation of 0.05 gave a standard range for women of 0.48 to 0.58 The distribution curve of the build of women, however, was more platykurtic, and the greater frequency of very narrow types depressed the measures of central tendency Seventeen per cent of men and 31 per cent of women had a chest circumference less than one-half their height (linear or slender build, under 0.50), and 12 per cent of both men and women had chests much larger than one-half their height (lateral or broad build, over 0.59) Actually there are as many extremely broad builds among women as among men

Changes in Chest Circumference and Body Build with Age—The men showed a gradual increase in chest circumference up to 50 years of age At 20 years the average chest circumference was 34 to 35 inches

(86.36 to 88.9 cm) This average increased to 37 or 38 inches (91.44 or 96.52 cm) at the end of the fourth decade and remained at 37 inches with only a slight tendency to decrease in the very old men. None of the extremely large chests occurred in the very old age groups. This fact suggests for the men with large chests a high death rate in the previous decades. The women showed a similar rise from 32 inches (81.28 cm) at the age 20 to 35 inches at the end of the fifth decade, after which there was a tendency toward decrease in chest circumference.²²

The chest/height ratio also showed the tendency observed in the case of chest circumference²³ (table 2). The ratio of the men showed a definite tendency to rise from an average of 0.51 (the height roughly twice the chest circumference) at 20 years to 0.55 at age of 40 years. The slight rise after this age was probably due to additional deposition of fat over the chest. Among the women the chest/height ratio was similarly increased with age. The increase was gradual up to the age

TABLE 2—Ratio of the Mean Chest/Height Ratio at Various Ages

Age Groups	15 to 19	20 to 24	25 to 29	30 to 34	35 to 39	40 to 44	45 to 49	50 to 54	55 to 59	60 to 64	65 to 69	70 and Over	All Ages
1,861 men	0.486	0.512	0.524	0.531	0.540	0.550	0.553	0.556	0.559	0.551	0.546	0.560	0.543
1,797 women	0.501	0.504	0.507	0.516	0.532	0.545	0.563	0.561	0.553	0.558	0.554	0.519	0.532

of 35, after which it became more rapid. This rapid rise in middle age was probably due to the influence of deposition of fat. As will be shown in another study,¹⁸ this disposition is in itself related to build and does not appreciably affect the division of the linear and the lateral type by the chest/height ratio. Except in a few abnormally obese persons, the deposition of fat over the chest does not change the index by more than 0.02 unit.

22 The following coefficients of correlation of age with chest circumference were obtained

Men	Women
$r = 0.216 \pm 0.022$	$r = 0.360 \pm 0.021$
$\eta = 0.324$	$\eta = 0.408$
$\xi = 0.058 \pm 0.011$	$\xi = 0.036 \pm 0.009$

Thus, the correlations were fairly good, though decidedly nonlinear. There was definitely a growth in the chest circumference during the third decade of life.

23 The following coefficients of correlation of age to chest/height ratio were obtained

Men	Women
$r = 0.244 \pm 0.022$	$r = 0.400 \pm 0.020$
$\eta = 0.318$	$\eta = 0.430$
$\xi = 0.041 \pm 0.009$	$\xi = 0.025 \pm 0.007$

As was true with chest circumference, the correlation was nonlinear, though in the case of chest/height ratio the correlation was more linear than in that of chest circumference. The correlation for the women was far more significant and more linear. This again was probably due to the steadier accumulation of fat on the chest after age of 35 years, when the curve for men tends to level off.

Relation of Build to Blood Pressure—There is a significant statistical relation between body build and systolic pressure. In the group of 1,861 men there was a steady rise in mean systolic pressure as the build progressed toward the lateral extreme (table 1). Those with very linear builds (chest/height ratio of 0.47 and under) showed an average pressure of 114 mm. This average rose to 120 mm in the group with intermediate builds and rose further to 130 mm in the group having very lateral builds. That this is not an artefact produced by a small number of hypertensive persons of lateral build is shown by the fact that the median and modal pressures followed the same tendency, and both rose from 110 mm in persons of linear build to over 118 mm in those of lateral build.

Diastolic pressure shows the same relation to build as does systolic pressure (table 1). With a progression toward the lateral extreme there was an increase in both the mean and the modal pressure. The mean diastolic pressure for the men of very linear build was around 70 mm, whereas those of the lateral type showed an average diastolic pressure of around 79 mm. The median and modal diastolic pressures rose from 70 mm in the men of linear build to over 77 mm in those of lateral or broad build.

The group of 1,797 women showed a similar tendency. Those of the linear type of build had systolic pressures under 110 mm on the average, while those of the lateral type showed an average systolic pressure of almost 130 mm. The mean, median and modal systolic pressures all showed the same tendency to rise as the frame widened.²⁴

The female group showed a similar difference in diastolic pressure between persons of narrow and those of broad builds. The women of very linear build averaged a diastolic pressure of less than 67 mm, slightly lower than that of the men of linear build, while the women of lateral build averaged a diastolic pressure of around 77 mm. The

24 The correlations between chest/height ratio and systolic pressure were significant and positive (table 1). That for the male group was only insignificantly nonlinear, while that for the female group was definitely linear. The greater significance of the correlation for the female group may be explained on the basis of the previously noted accumulation of fat. For the female group the correlation of chest/height to weight was 0.70, which is 0.09 greater than the corresponding correlation for the male group. These observations indicate that the females of lateral build are subjected to the hazard of obesity to a greater extent than are the males. This is borne out by the fact that with weight held constant the partial correlations of chest/height to systolic pressure show a significant difference. The partial correlations observed in this study were as follows:

Men $r_{cs\ w} = 0.100$

Women $r_{cs\ w} = 0.199$

median and modal diastolic pressures exhibited the same tendency to rise as the build broadened toward the lateral extreme ²⁵

Distribution of Low and High Pressures in Build Groups—A comparison of the distributions of the low and high pressures among the persons of linear as contrasted with those of lateral build is more revealing. Only 4 per cent of the male group with linear build had systolic pressures over 140 mm, while 22 per cent with lateral build were definitely hypertensive (fig 2). Similarly, only 2 per cent of the women with linear, or thin, build had systolic pressures over 140 mm, while 27 per cent of the women with lateral, or broad, build were hyper-

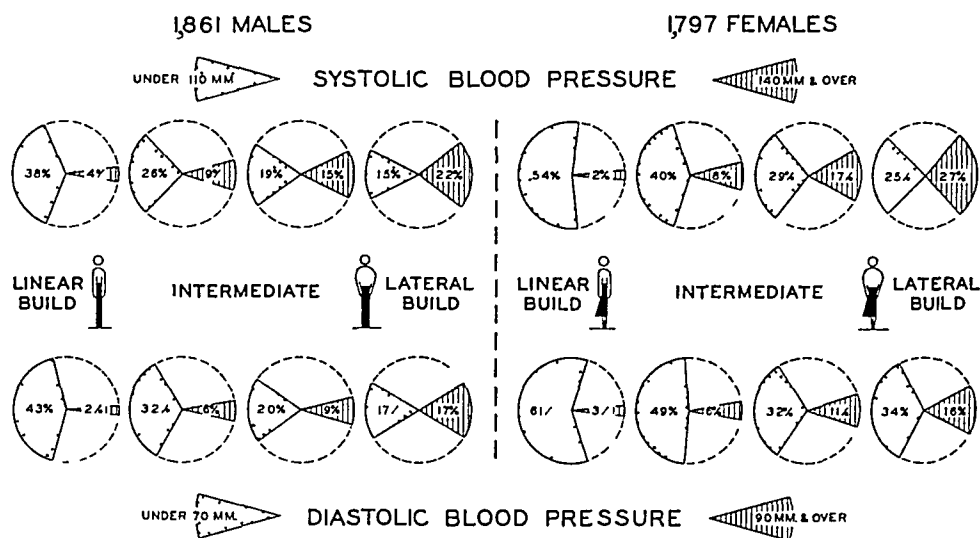


Fig 2—Comparative distribution of low and high pressures in various body build groups. Viewed in the direction from the linear to the lateral build, the cross-hatched sections show the increase in the incidence of hypertension, whereas the dotted sections show the decrease in the incidence of low pressure. This holds true for both the male and the female sex and for diastolic as well as systolic pressure. (Chart prepared by W. P. A.)

25 The correlations between chest/height ratio and diastolic pressure show a significant relation (table 1). At first glance it might seem that the male-female reversal of linearity relations is a contradiction of the explanation given in footnote 24 concerning the systolic correlation. However, in the first place the tendency for diastolic pressure to correlate with the chest/height ratio is the same, though not as marked, secondly, the correlation for neither the male nor the female group is significantly nonlinear. The explanation for the small degree of difference between correlations for men and women given in footnote 24 would be correct for the difference in the diastolic correlation only if the correlation of diastolic pressure to weight for the female group was almost identical to that for the male group. Actually, for the female group the correlation of diastolic pressure to obesity is 0.22, identical with the corresponding correlation for the male group, while in the case of the correlation of systolic pressure to obesity that for the female group at 0.18 is only 0.02 greater than that for the male. This fact also explains the greater (though not significant) test for linearity in the diastolic correlation for the female group.

tensive The relation was reversed in respect to the low pressures Among the persons of linear build, 38 per cent of the men and 54 per cent of the women had systolic pressures under 110 mm, while among those of lateral build only 15 per cent of the men and 25 per cent of the women had the same low systolic pressures

The comparison of the distributions of low and high diastolic pressures gives results similar to those involving the systolic pressures In figure 2 it is seen that whereas only 2 per cent of the persons of linear build had high diastolic pressures, 17 per cent of those of lateral build had diastolic pressures over 90 mm This contrast speaks for an unusual difference in susceptibility to hypertension among persons of the contrasting extremes of body build Conversely, 43 per cent of the men of linear build and only 17 per cent of those of lateral build had low diastolic pressures, while 60 per cent of the women of linear build and only 34 per cent of those of lateral build had diastolic pressures under 70 mm Thus it is apparent that the low pressures are predominantly found in persons of linear build and the high pressures in those of lateral build Just as important as this association is the fact that the person of the linear type of build tends to repel high pressure and the one of the lateral type tends to repel low pressure

Thus far the differences in the incidence of high and low pressures within specific body build groups have been observed This was done by holding the build constant and making the pressure the dependent variable If the correlation actually holds true, there should be a similar difference in the incidence of linear and lateral builds within the specific blood pressure groups Data obtained with blood pressure held constant and with build as the dependent variable will now be presented

That this association is applicable in either direction is illustrated in figure 3, in which the groupings are reversed Of the persons with low systolic pressure, 28 per cent of the men were of linear build while only 8 per cent were of lateral build, similarly, 40 per cent of the women were of linear build while only 8 per cent were of lateral build Conversely, of the hypertensive men, only 6 per cent were of the linear type while fully 24 per cent were of the lateral type, and of the hypertensive women, 8 per cent were of the linear type while 41 per cent were of the lateral type

In the case of diastolic pressure the relations are similar Of the persons with low diastolic pressure (under 70 mm), there was in the male group a great difference in representation of the two extreme types of build, for 26 per cent were of linear build and only 7 per cent were of lateral build In the female group 39 per cent were of linear build and 9 per cent of lateral build Conversely, of the persons with high diastolic pressure (over 90 mm), 25 per cent of the men were of the

lateral type while only 3 per cent were of the linear type, and 37 per cent of the women were of the lateral type while only 8 per cent were of the linear type. The data indicate, therefore, that in any group with low pressures the incidence of linear builds is far greater than that of lateral builds, and that in any group with high pressures the incidence of lateral builds is far greater than that of linear builds.

The ratio of actual to expected incidence²⁶ demonstrates in another way the same tendency for low pressure to be associated with linear build and high pressure with lateral build. The ratio was calculated

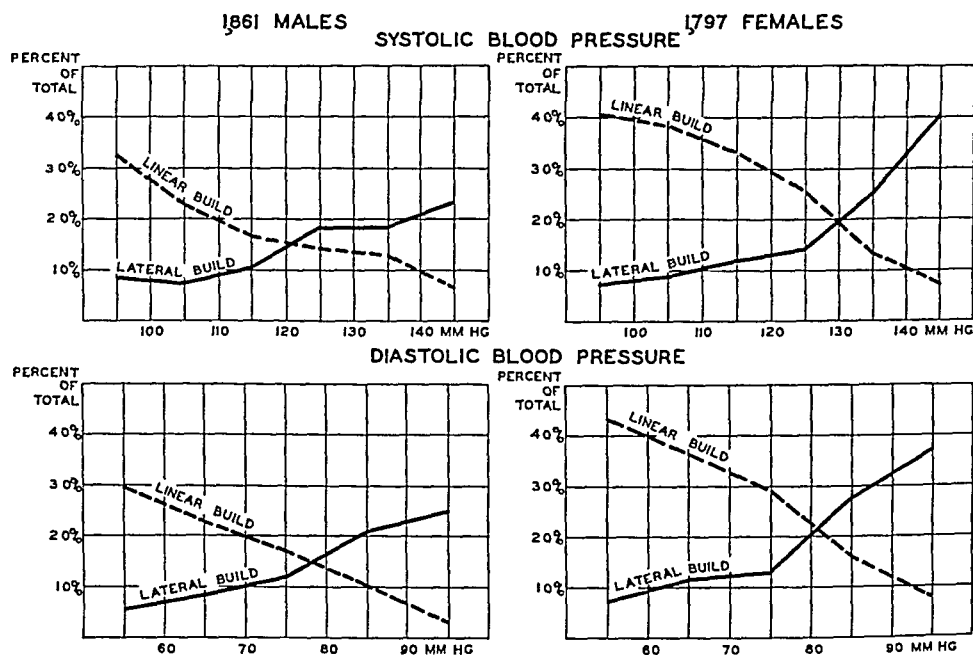


Fig 3—Comparative distribution of build at various levels of blood pressure. Linear build is most common in the low pressure groups, in which lateral build is comparatively rare. Lateral build is most common in the high pressure groups, in which linear build is comparatively rare. (Chart prepared by W P A.)

26 The ratio of per cent actual to expected incidence is simply calculated and is of use in illustrating the relative effect of the extremes of one array on the dispersion of another correlated array. The technic is used here to show the unusual influence of a broad build on blood pressure. For example, if, in any random group of 100 men, 22 are of the linear type of build and 13 are of the lateral type, and if there is no correlation of build to blood pressure, then the same ratio of 22 linear to 13 lateral should hold true in any group of persons whether they have low, medium or high pressures. This, however, is not the case. Among a group of 100 hypertensive persons, there are actually only 9 of the linear type as compared to 23 of the lateral type. This gives a ratio of actual to expected incidence of $9/22$, or only 41 per cent of the expected incidence of linear build among hypertensive persons, as compared with the ratio of $23/13$, or 177 per cent of expected incidence of lateral build among hypertensive persons. Simply stated, this means that among hypertensive men lateral build predominates in a ratio of over 4 : 1.

separately for each body build-pressure group so as to illustrate the comparative differences in the expectancy of high and low pressure and to standardize the variations in the incidence according to types of build. Since there were 22 per cent linear builds to only 13 per cent lateral builds, the ratio of actual to expected ratio corrects for this uneven distribution. The ratio was consistent with differences in the blood pressure that were observed in comparisons of the measures of central tendency of distribution and in the comparisons of incidence within specific body build-pressure groups.

A comparison of the ratios of actual to expected incidence was first made for the groups having extreme build (table 3). The men of lateral build, or the broad-chested type, had more than four times the expectancy of systolic hypertension that the men of linear build, or the

TABLE 3—*Ratio of Actual to Expected Incidence of Body Build (Measured By Chest/Height) According to Systolic Pressure**

Type of Build	1,861 Men Blood Pressure			1,797 Women Blood Pressure		
	Low	Moderate	High	Low	Moderate	High
Linear	148	87	39	128	90	26
Intermediate	91	103	106	89	106	104
Lateral	62	108	177	57	107	293

*For this and subsequent tables, the following classifications are used: low systolic pressure under 110 mm., moderate systolic pressure, 110 to 139 mm., high systolic pressure 140 mm. and over, low diastolic pressure, under 70 mm., moderate diastolic pressure, 70 to 89 mm., high systolic pressure, 90 mm. and over, linear body build, chest/height ratio under 0.51, intermediate body build, chest/height ratio of 0.51 to 0.58, lateral body build, chest/height ratio of 0.59 and over.

In comparing the observed distributions, chi square was below the 0.0001 per cent level of significance.

narrow-chested type had, and less than one-half the expectancy of low pressure. The difference was even more striking among the women. The women of lateral, or broad, build had an almost eleven times greater expectancy of high systolic pressure than the women of linear build and less than one-half the expectancy of low pressure.

Another illustrative comparison is of the ratios of actual to expected incidence made between groups with extreme pressure within each group representing types of body build. In any random series of 100 men of lateral build there should be 3 with systolic hypertension to every 1 person with low pressure. A group of women of lateral builds would show an even more striking difference. 5 would be hypertensive to every 1 who had low pressure. The situation is reversed in the groups with linear, or narrow-chested build. The men of linear build would have 5 persons with low systolic pressure for every 2 with high pressure. The women of linear build would have 5 persons with low systolic pressure to every one with high systolic pressure.

In the case of diastolic pressure the ratio shows similar tendencies (table 4) Comparison first of the groups having the extreme types of build shows the men of the lateral, or the broad, type to have more than seven times the expectancy of diastolic hypertension than the men

TABLE 4—Ratio of Actual to Expected Incidence of Body Build (Measured By Chest/Height) According to Diastolic Pressure *

Type of Build	1,861 Men Blood Pressure			1,797 Women Blood Pressure		
	Low	Moderate	High	Low	Moderate	High
Linear	148	83	26	123	82	33
Intermediate	91	103	108	89	109	106
Lateral	62	115	192	71	121	264

* Same footnote as for table 3

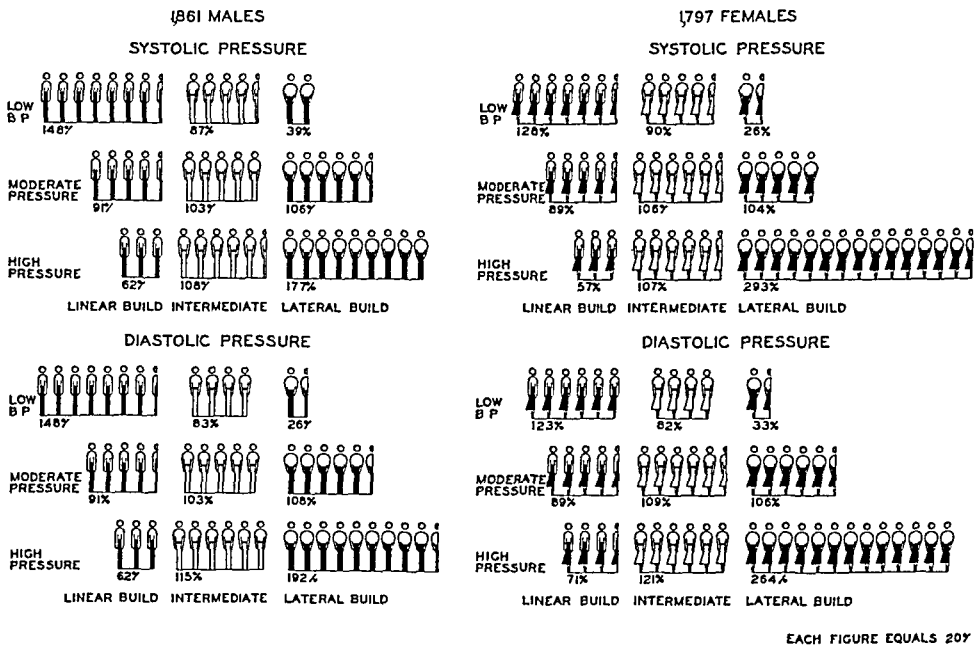


Fig 4—Influence of body build on blood pressure, showing the per cent ratio of actual to the expected incidence (see text), which illustrates the comparative association of low and high pressures with linear and with lateral build Linear build has the greatest representation in the group with low pressure and the smallest representation in the group with high pressure Conversely, lateral build has the greatest representation in the group with high pressure and the smallest representation in the group with low pressure (Chart prepared by W P A)

of linear build and less than one-half the expectancy of low diastolic pressure The women of lateral build are shown to have eight times the expectancy of diastolic hypertension that women of linear build have and only slightly more than one-half the expectancy of low pressure

A second comparison of the ratio of actual to expected incidence for the groups with extreme pressures within each build group shows that in

any random group of men of lateral build there would be 3 with high diastolic pressures to every 1 with low pressure (table 4) In a random group of women with lateral pressure there would be 7 with high diastolic pressures to every 2 with low diastolic pressures In the groups with linear or slender build the situation is reversed A group of men of linear build would include 6 with low diastolic pressure to every 1 with high diastolic pressure, and a group of women of linear build would have 3 persons with low pressure to every one with high pressure (fig 4)

It is apparent from this evidence that as the group progresses toward the lateral, or broad-chested, build the chances of hypertension developing become progressively greater, and the chances of a low pressure developing become progressively smaller

TABLE 5—*Mean Systolic Pressure of Persons of Various Builds in Each Age Group*

Subjects Studied	Type of Build	Age Groups								
		20 to 24	25 to 29	30 to 34	35 to 39	40 to 44	45 to 49	50 to 54	55 to 59	60 and Over
1,861 men	Linear	118	117	111	113	114	110	113	119	128
	Intermediate	120	118	116	116	118	121	124	125	132
	Lateral	120	120	122	120	121	127	124	138	136
1,797 women	Linear	107	105	109	111	114	112	119	125	138
	Intermediate	106	108	111	113	117	123	121	134	142
	Lateral	123	113	116	120	124	130	125	155	155

Age as a Factor in the Relation of Body Build to Blood Pressure —

The age factor has not yet been taken into consideration Table 5 shows that the tendencies which have already been pointed out roughly hold true at every age Among our subjects, at every age the persons of broad build showed a higher pressure than the persons of narrow build This should not be surprising In a previous paper it was reported that the hypertensive pressures in older persons almost invariably occur among those who in youth had slightly elevated pressures Hence, though the difference might not be so great in young men as in older ones, it should be apparent As concerns systolic pressure the men of linear build as well as those of intermediate build showed a slightly decreased pressure during the fourth decade This phenomenon has been noticed in most of the studies on the systolic blood pressure of young men²⁷ Aside from this change, the men with linear build did not show an increased systolic pressure until late in life Those with the lateral type of build began adult life with a higher systolic pressure and an

27 (a) Alvarez, W C, Wulzen, R, and Mahoney, L J Blood Pressures in Fifteen Thousand University Freshmen, *Arch Int Med* **32** 17 (July) 1923

(b) Johnson, W M Tobacco Smoking Clinical Study, *J A M A* **93** 655 (Aug 31) 1929

early increase to very high levels. The women of linear build did not show an appreciable increase in systolic pressure until after the age of 50 years. The women of the lateral type were already registering average pressures of over 120 mm when they were 40 years of age. In every age group the women of lateral build showed a higher mean systolic pressure.

TABLE 6—*Mean Diastolic Pressure of Persons of Various Builds in Each Age Group*

Subjects Studied	Type of Build	Age Groups								
		20 to 24	25 to 29	30 to 34	35 to 39	40 to 44	45 to 49	50 to 54	55 to 59	60 and Over
1,861 men	Linear	71	71	70	72	73	71	72	74	72
	Intermediate	73	70	72	73	75	76	77	77	77
	Lateral	75	80	77	77	79	78	77	83	77*
1,797 women	Linear	64	64	67	68	70	70	75	75	75
	Intermediate	64	66	68	70	72	75	74	77	81
	Lateral	73	70	73	74	76	77	75	88	83

* Insufficient distribution—less than 15 persons

TABLE 7—*Incidence of Low and High Systolic Pressures in Persons of Linear and Lateral Builds in Various Age Groups*

		Age Groups and Body Build									
		20 to 29		30 to 39		40 to 49		50 to 59		60 and Over	
		Linear	Lateral	Linear	Lateral	Linear	Lateral	Linear	Lateral	Linear	Lateral
1,861 men	Percentage incidence of low pressures (under 110 mm)	28	17	45	15	45	18	40	14	17	3
	Percentage incidence of high pressures (140 mm and over)	4	8*	3	8	3	16	4	22	17	39
1,797 women	Percentage incidence of low pressures (under 110 mm)	65	18	51	34	42	24	35	20	17*	7
	Percentage incidence of high pressures (140 mm and over)	0	0	1	16	5	24	14	40	50*	57

* Insufficient distribution—less than 15 persons. In comparing the observed frequencies in linear and lateral build, chi square is below the 1 per cent level of significance, this is true for each age group.

In the case of diastolic pressure the age factor shows similar tendencies (table 6). The mean diastolic pressure, except in two erratic groups, was consistently higher in the men and women of lateral or broad, type than in those of the linear, or slender, type. The men of linear build maintained about the same pressure throughout life, while the men of lateral build tended to show an increasing pressure. The

women of both types showed an increase in mean pressure, but those of lateral build showed an increase to a greater extent and on a higher level

The incidence of low and of high systolic pressure in the various age groups is more illustrative of the differences in distribution (table 7). The incidence of low systolic pressure was very high among persons of linear build in all age groups as compared with a low incidence among the persons with lateral build.

This difference was least marked in men before 30 years and very striking until the age of 60, after which it became very marked. In the women it was most marked under 30 years and decreased somewhat

TABLE 8—*Incidence of Low and High Diastolic Pressures Among Persons of Linear and Lateral Builds in Various Age Groups*

		Age Groups and Body Build									
		20 to 29		30 to 39		40 to 49		50 to 59		60 and Over	
		Linear	Lateral	Linear	Lateral	Linear	Lateral	Linear	Lateral	Linear	Lateral
1,861 men	Percentage incidence of low pressures (under 80 mm)	43	8*	40	23	42	19	32	16	44	15
	Percentage incidence of high pressures (90 mm and over)	1	0*	0	6	2	17	0	16	11	12
1,797 women	Percentage incidence of low pressures (under 70 mm)	70	36	61	43	46	33	31	22	33*	7
	Percentage incidence of high pressures (90 mm and over)	0	0	1	11	4	16	10	22	17*	29

* Insufficient distribution—less than 15 persons. In comparing the observed frequencies in linear and lateral build, chi square is below the 1 per cent level of significance, this is true for each age group.

later in life. This is probably due to the very strong tendency for young women to have low pressures regardless of their build. Conversely, the incidence of high systolic pressure was lowest among the persons of linear build (only after the sixtieth year does it rise in men), while the incidence of high systolic pressure among the men and women of lateral build steadily increased with each decade.

The incidence relations in diastolic pressures (table 8) show much the same tendencies as were observed in systolic pressure. In every age group studied low pressure predominated among the men and women of linear build and high pressure predominated among those of lateral build. The incidence of high diastolic pressures in the men of linear build was constant until very late in life, in the women it slowly rose but became significant only after the age of 50. The incidence of low pressures was nearly constant in the men of linear build throughout life. It is well known that any group of women will have a greater

incidence of the lower pressures than men in the younger age groups, this is especially true of slender women. Consequently, the decreases with advancing age in the incidence of low pressures in women of linear build is to be expected. Among the broad-chested men and women the incidence of low pressure decreased after the age of 30, while the incidence of high pressures increased.

COMMENT

In order to determine what relation exists between a person's build and his blood pressure, we have statistically analyzed the periodic health examination records of 3,658 persons. A simple ratio of width to height, calculated in terms of chest circumference divided by the standing height, was used. With this index the persons were divided into groups of (1) a linear, or slender, type of build, consisting of those with very narrow chests, (2) of a lateral type of build, those with very broad chests, and (3) of an intermediate type of build. This distinction of the persons of extremely broad build from those of extremely narrow build is obvious even to clinicians who have never formally applied anthropometric technics. It must be remembered that in making gross morphologic divisions, such as linear and lateral, only the beginnings of anthropometry are involved. To be sure, hypertension will appear in persons of both types, but for every person of narrow build having hypertension there will be 7 persons of broad build. For each of the persons of linear, or slender, build having a high pressure there will be 10 persons of linear build having pressures under 110 mm. It is true that among a group with broad lateral builds some will have low pressure. This does not vitiate the relation of hypertension and lateral build, because for every person of lateral build with low pressure there will be 4 of lateral build with high pressures.

That there is a correlation between body build and blood pressure should not be surprising. The clinical impression of the hypertensive persons has always been of a large, broad-chested person. However, this impression has always been confused with that of obesity. From a study already published,²⁸ it is apparent that observations made with measurements of weight held constant show the association of hypertension with lateral build to be even more striking than the well known association of hypertension with obesity.²⁸ It would seem from the

28 The partial correlation of chest/height to systolic blood pressure with weight held constant is $r_{cs.w} = 0.100$, the partial correlation of weight to systolic blood pressure with chest/height held constant is $r_{cs.w} = 0.077$. In other words, the more significant correlation is between chest/height and systolic blood pressure. A complete analysis of the obesity-hypertension relation is presented in an article, "Obesity and Hypertension" by S. C. Robinson, M. Brucer and I. Mass (J. Lab. & Clin. Med. 25: 807, 1940).

additional fact that obesity itself has a strong association with build, that the obesity-hypertension relation is really to a great extent a build-hypertension relation

With the morphologic habitus thus definitely proved to be a part of the syndrome of hypertension, the first and most obvious implication is that hypertension must be a hereditary phenomenon. Baldwin's²⁹ work with the growth characteristics of children and Davenport's¹² work with inheritance and build firmly established the widely known fact that the structure of the body is an inherited characteristic. Since in this paper hypertension has been shown to be correlated to the lateral, or broad, build and low pressure to the linear, or thin, build, the hereditary predisposition to normal pressure and hypertension must be considered an established fact.

If heredity is the main determinant of body build and if human constitution in turn is correlated to hypertension, it would be interesting to contemplate which build more truly represents the human biologic and evolutionary pattern. In other words, what is the normal build? Purely statistical reasoning on contemporary series would choose the modal, or intermediate type. If this is correct, then both the lateral and the linear build group should be looked on as equally deviant from the true normal. On the other hand, Gildea, Kahn and Mann¹⁰ and others have expressed the opinion that the lateral build is more truly representative of the human race. In this case the person of linear, or thin, build is the deviant. This implies that man's original frame was of the lateral type, and studies of early man support this view. Reconstructions of the paleolithic man show him to have been short and stocky, emphasizing a kinship to our higher simian ancestors. The linear build would then represent evolutionary changes away from the broad pattern. Such considerations of the biologic place of the respective builds of man, especially as they relate to the evolutionary scale, may throw light on the classification of disease and possibly on its causes. The study of the trend of disease in the evolution and growth of the human species may lead to valuable contributions in the elucidation of the origins of hypertension. In this respect a study of the disease picture among primitive peoples would be helpful.

In any case, whichever build represents ascent or descent in the evolutionary scale, it is safe to say that from the standpoint of longevity, the linear build is more desirable. There is substantial statistical evidence that the person with lateral build does not reach old age as frequently as does the one with linear build. In our own data the mean, the median and the modal chest circumference reach a peak at about the sixth decade and then decrease. None of the extremely large chests

²⁹ Baldwin, B. T. *The Physical Growth of Children from Birth to Maturity, Studies in Child Welfare*, Iowa City, University of Iowa, 1921, vol. 1, no. 1.

are observed in the older age groups. A consideration of the diseases to which each build group is predisposed seems to lend support to this conception. Obesity, which is positively associated with an increased mortality, is a much greater hazard of the group with lateral build than of that with linear build.³⁰

Practically all of the cardiovascular diseases, especially hypertension, and their accompanying high mortality, occur more frequently in persons of the obese and lateral types. It is therefore clear that the person of linear build will outlive the one of lateral build. On the other hand, while the person of lateral build dies early, it is contended by some writers that he lives a more efficient life. The diseases associated with lateral build are not the diseases that cripple the patient's efficiency during his most productive years. The impression has already gained headway that the person of the linear build and low pressure type "lives long but lives miserably." There is no proof for such a statement. More study of the diseases in each build group is necessary.

It would be well, not only from the standpoint of clinical research but also from that of practical medicine, to bring together for coordinated study data on the diseases that seem to occur predominantly in persons of select body build groups. For example, the lateral type of body build accompanied by obesity is intimately associated with diseases of the myocardium and the circulatory system³¹ with arteriosclerosis,³² with diabetes³³ and with toxemia of pregnancy³⁴. These few by no means exhaust the list. On the other hand, the person of linear build is most often underweight. He tends to be immune to the diseases associated with the lateral build. He is susceptible to gastroduodenal ulcer and dyspepsia,³⁵ to exophthalmic goiter and neurocirculatory asthenia,³⁶ to

30 The coefficient of correlation of chest/height ratio to weight was 0.612 ± 0.014 for the male group and 0.708 ± 0.014 for the female group.

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33 (a) Joslin, E. P. *Treatment of Diabetes Mellitus*, ed. 6, Philadelphia, Lea & Febiger, 1937. (b) Master, A. M., and Oppenheimer, E. L. A Study of Obesity. Circulatory, Roentgen-Ray and Electrocardiographic Investigations, J. A. M. A. **92** 1652 (May 18) 1929. (c) Gottschick, J. Constitutional Pathological Observations in a Family with Diabetic Members, *Ztschr. f. menschl. Vererb- u. Konstitutionslehre* **19** 585, 1935.

34 Herrick, W. W., and Tillman, A. J. B. The Mild Toxemias of Late Pregnancy (Their Relation to Cardiovascular and Renal Disease), *Am. J. Obst. & Gynec.* **31** 832, 1936.

35 Robinson, S. C. Exophthalmic Goiter and Gastroduodenal Ulcer. Two Constitutionally Different Diseases with Note on Pernicious Anemia, *Illinois M. J.* **73** 210, 1938.

36 Crile, G. *Diseases Peculiar to Civilized Man*, New York, The Macmillan Company, 1934.

migraine³⁷ and to some neuroses³⁸ Rheumatism, anemia and various "general infections" have also been found to be characteristic anomalies of persons of linear build³⁹ Visceroptosis has long been known to be a part of the asthenic picture⁴⁰

The constitutional habitus is not the only common factor determining the classification of these diseases Emotional conflict is common to the group with linear build that has ulcer, goiter, asthenia and migraine Even more basic physiologic properties are possibly correlated to build Investigators have found differentiations in types of build on the basis of blood chemistry levels,⁴¹ acid-base equilibrium and basal metabolism,⁴² reactions to drugs,⁴³ color and form reaction,⁴⁴ and behavior patterns⁴⁵ As Cohen⁴⁶ pointed out, "there seems to be an intimate relation between biochemical, anatomical and mental changes"

It is not to be inferred that the type of build as such causes disease Not every patient with lateral build is hypertensive or even potentially hypertensive It can be seen, however, that the various morphologic

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38 (a) Kretschmer, E *Physique and Character*, translated by W J H Sprott, New York, Harcourt Brace and Company, Inc, 1926 (b) Brandt, W *The Biological Differences Between Pyknics and Leptosomes*, *Deutsche med Wchnschr* **62** 501, 1936

39 (a) Edens, E *Constitution as a Basis for Disease*, *Klin Wchnschr* **17** 433, 1938 (b) Davenport¹²

40 (a) Osler, W *The Principles and Practice of Medicine*, ed 13, revised by Henry A Christian, New York, D Appleton-Century Company, Inc, 1938 (b) Tice, F *Practice of Medicine*, Hagerstown, Md, W F Prior Company, Inc, 1928, vol 6 (c) Musser, J H *Internal Medicine*, ed 2, Philadelphia, Lea & Febiger, 1934 (d) Fossier, A E Cause of Essential Hypotension, *Am J M Sc* **171** 496, 1926 (e) Backer^{7a} (f) Crile³⁶

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43 Hertz, T *Pharmacodynamic Investigations on Constitutional Types*, *Ztschr f d ges Neurol u Psychiat* **134** 605, 1931

44 Lindberg, B J *Experimental Studies of Colour and Non-Colour Attitude in School Children and Adults, Especially with Regard to Its Condition in Different Types According to Individual Psychology of Sjöbring and Anthropometric Index of Stromgren, Together with Two Psychological Tests*, *Acta psychiat et neurol*, 1938, supp 16, pp 1-170

45 Wertheimer, F I, and Hesketh, F E *Significance of Physical Constitution in Mental Disease*, *Medicine* **5** 375, 1926

46 Cohen, I I *Determinants of Physique*, *J Ment Sc* **84** 495 1938

builds carry different disease potentialities and disease immunities As Draper ^{47a} put it, the "physical features express in the morphologic panel certain basic hereditary influences" It is with these basic disease potentialities and immunities that the astute physician should be familiar in order to help unravel the mystery of hypertension and other equally elusive diseases Before the medical profession can truly understand the degenerative diseases it will be necessary to relate them to morphologic physiology and personality and to study man as a whole together with his new environmental surroundings The study of types of body build is only the beginning Draper ^{47b} stated "In itself, the study of human morphology adds perhaps but little, as a means to the larger conception of the man as a whole, it is well nigh indispensable"

This approach would suggest that the study of hypertension does not belong to the province of any one division of medicine but is a problem of the whole of clinical medicine Hypertension is not an isolated degeneration that strikes a chance selection of persons after their fortieth year It is a slow insidious degenerative and metabolic change, "an important morbid state of the body" confined for the most part to a predisposed type Since hypertension is rare in many primitive tribes it would seem that it appears after the susceptible person has exposed himself for a sufficiently long time to the harmful environmental influences inherent in civilized life, the outstanding one of which is sedentary living

SUMMARY AND CONCLUSIONS

A review of the literature shows that no rigidly controlled statistical study on a sufficiently large series has conclusively established a positive correlation between blood pressure and body build Some writers contend that no correlation whatsoever exists

In this study of blood pressure and body build made on 3,658 persons, an index derived from dividing the chest circumference by the standing height was used as a ratio of width to height to distinguish the narrow linear type of persons from the broad lateral type

Among 1,861 men and 1,797 women, 17 per cent of the men and 31 per cent of the women were of the narrow-chested, linear type of build while 12 per cent of both men and women were of the broad-chested lateral type of build

Observations lead both to the general conclusion that a positive correlation between body build and blood pressure does exist and to the following specific conclusions

In both men and women there is an increase in the average build—chest/height ratio—with an increase in age This increase in the adult

47 (a) Draper, G, Dunn, H L, and Seegal, D Studies in Human Constitution I Clinical Anthropometry, J A M A 82 431 (Feb 9) 1924 (b) Draper, G Disease and the Man, New York, The Macmillan Company, 1930

is greatest before the age of 50 years. after this age there is a tendency for the average build to decrease

Men and women of lateral, or broad build show a marked tendency to hypertension. The mean, median and modal systolic and diastolic blood pressures increase with an increase in chest/height ratio

The lateral, broad-chested type of men have more than four times the expectancy of systolic hypertension developing and seven times the expectancy of diastolic hypertension developing as have the men of linear, or slender, build. The women of lateral build have almost eleven times the expectancy of systolic hypertension developing and eight times the diastolic hypertension developing as have the women of linear build

The men and women of lateral build have only about one-half the expectancy of having a low systolic or diastolic pressure as have men and women of the linear, or slender, build

In any random group of men of lateral build the ratio of high systolic and diastolic pressures is three times that of low pressures. In any random group of women of lateral build the ratio of high systolic pressure is five times greater than that of low systolic pressures, and the ratio of high diastolic pressure is four times greater than low diastolic pressure

In any random group of men of linear build the ratio of low systolic pressure is three times that of high pressure and the ratio of low diastolic pressure is five times that of high pressure. In the group of slender women the ratio of low to high systolic or diastolic pressures is 4 : 1

In any random group of persons with systolic hypertension the ratio of lateral to linear builds will be for the men, 4 : 1, for the women, 11 : 1. In any random group of persons with diastolic hypertension the ratio of lateral to linear builds will be for the men, 7 : 1, for the women, 8 : 6

In any random group of persons with low systolic pressures the ratio of linear to lateral builds for both men or women will be more than 2 : 1. In those with low diastolic pressure the corresponding ratio for men will be more than 2 : 1 and for women, almost 2 : 1

The relation between lateral build and hypertension and between linear build and low blood pressure is found in all age groups

The incidence of high pressures increases and low pressures decreases with age in men of lateral build. In those of linear build the incidence of high pressure is constant up to the seventh decade, the incidence of low pressure is constant throughout life

The incidence of high pressures increases with age more markedly among women of lateral build than among those of linear build, and at every age the incidence of low pressure is greatest among the women of linear build

DIAGNOSIS AND TREATMENT OF GONORRHEAL SEPTICEMIA AND GONORRHEAL ENDOCARDITIS

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A discussion of gonorrheal endocarditis and gonococcemia seems timely for three reasons

1 There is increased interest in the disease, the large number of recent papers on the subject have made physicians aware that the condition is by no means uncommon. It has been said to comprise 11.6 per cent of all cases of bacterial endocarditis,¹ and one report stated that of cases of acute endocarditis studied at autopsy 26 per cent were of gonococcic origin.²

2 At present the diagnosis is either missed or not made until the disease, the mortality of which is extremely high, has been rampant for several weeks. It may be well to call attention to certain aids in diagnosis in the hope that the physician may at least suspect the presence of the condition before a blood culture positive for gonococci is obtained.

3 The introduction of fever therapy and the use of sulfanilamide and its derivatives have given means with which to combat gonorrheal infections successfully. It is possible that early diagnosis and proper treatment may reduce the mortality in this the most serious complication of gonorrhea.

Fourteen cases are here reported. In 12 of these the diagnoses were proved at autopsy. In the other 2 cases the disease was not fatal, the presence of endocarditis was not proved, nor was the organism ever obtained from the blood stream. However, the evidence in favor of the diagnosis of gonococcic carditis was so strong that it is felt the cases should be included here. These are cases of precisely the type in which diagnosis should be made early so that specific treatment may be initiated promptly.

Read in part before the Section of Medicine of the New York Academy of Medicine May 17, 1938

1 Thayer, W. S. Cardiac Complications of Gonorrhea, *Bull. Johns Hopkins Hosp.* **33** 361, 1922

2 Williams, R. H. Gonococcic Endocarditis, *Arch. Int. Med.* **61** 26 (Jan.), 1938

In 2 cases the patients were seen by me, the records of other cases were obtained through members of the staffs of St Luke's, Bellevue, Presbyterian, New York and the New York Post-Graduate hospitals and the University of Virginia Hospitals. Data for 8 other cases of the disease recorded at the Mount Sinai Hospital are abstracted briefly in a separate table. Most of these 8 cases have been previously reported by Newman³ and others.

One case of probable gonococcemia occurring forty years after the initial infection is also summarized. The patient was recently discharged from St Luke's Hospital, to which he was admitted with a diagnosis of acute rheumatic fever.

In Cecil's textbook of medicine it is stated by George Blumer⁴ that recovery from gonorrheal septicemia occurs occasionally, and there are cases on record in which there was recovery from apparently obvious cardiac complications, but such cases are exceptional. Libman⁵ stated that while acute bacterial endocarditis is said to be fatal in all cases, he had gained the impression that acute gonococcic endocarditis had a better prognosis. Warfield,⁶ on the other hand, expressed the belief that recovery could not take place in a case of true gonococcic endocarditis.

Friedberg⁷ reported 4 cases of gonococcemia, in 1 of which gonorrheal endocarditis was probably also present. All of his patients recovered. He pointed out the importance of correct diagnosis and gave a table of what he considered important points in the differential diagnosis.

My report is presented not so much because 4 of the patients recovered but because I believe that it points out certain aids to diagnosis. The patients who recovered were not proved definitely to have gonorrheal septicemia. However, the evidence in favor of this diagnosis was so strong that it is felt there can be little doubt concerning it.

Jagić and Schiffner,⁸ and others⁹ have expressed the opinion that mild gonorrheal sepsis may occur with endocardial involvement and, not

3 Newman, A. B. Prognosis in Gonococcal Endocarditis. Review of Literature and Report of a Case with Spontaneous Recovery, *Am Heart J* **8** 821, 1932.

4 Blumer, G., in Cecil, R. L. A Text-Book of Medicine, Philadelphia, W. B. Saunders Company, 1927.

5 Libman, E. Affections of the Valves of the Heart, *M Clin North America* **1** 580 1917.

6 Warfield, L. M. Gonorrheal Endocarditis, *Wisconsin M J* **20** 578, 1921-1922.

7 Friedberg, C. K. Gonococcemia with Recovery, *Am J M Sc* **188** 271, 1934.

8 Jagić, N., and Schiffner, O. Ueber gonorrhoeische Herzerkrankungen, *Med Klin* **16** 976, 1920.

9 Baker, B. M., Jr., and Carter, E. P. Three Instances of Unusual Gonococcal Infection, *Bull Johns Hopkins Hosp* **50** 57, 1932.

infrequently, may be followed by complete recovery. They stated the belief that it was not necessary to isolate the organism from the blood stream to make the diagnosis.

The data for the 14 cases of gonorrheal sepsis that I have studied are given in table 1. Thirteen were thought to be cases of endocarditis and 1 was a case of pericarditis. Four cases are reported in detail: cases 6 and 7, in which death ensued, and cases 10 and 14 in which there was recovery.

REPORT OF CASES

CASE 6—L. F., a man, was admitted to the New York Post-Graduate Hospital on Sept 13, 1934 because of fever, malaise and articular pain of four weeks' duration. There was no history of gonorrhea or of previous heart disease. On his admission a systolic murmur was heard at the base of the heart, three days later a diastolic murmur was noted in the same region. On October 5 a systolic murmur was heard at the apex, and a notation was made to the effect that the

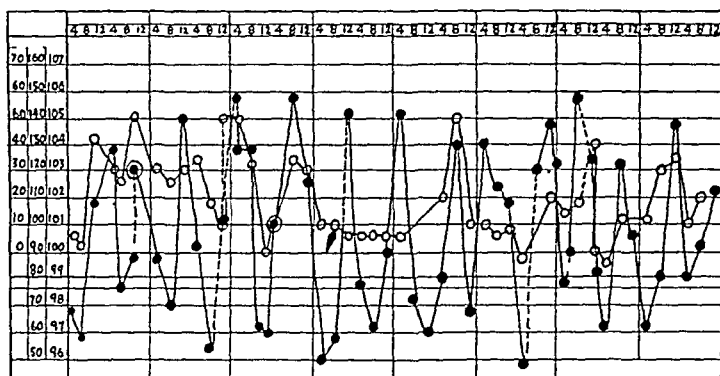


Fig. 1 (case 6)—Temperature (solid circles) and pulse (clear circles) recordings

murmurs were becoming rougher and louder. Nine blood cultures were sterile. The character of the temperature and pulse curves are shown in figure 1. It is worthy of note that there were two peaks daily for both curves, a point regarded by some physicians as of diagnostic importance. The gonococcus complement fixation was reported as doubtful, and a second specimen was requested. A positive blood culture was obtained on September 9, the organism being reported as the meningococcus, but on October 9 it was finally identified as the gonococcus. A presystolic murmur was heard on October 12. The spleen and liver were both palpably enlarged. Throughout his illness the patient complained from time to time of nausea and vomiting. Petechiae appeared at intervals. The electrocardiogram showed evidence of slight myocardial change. One transfusion of whole blood was given. The patient died on October 16. Autopsy revealed acute vegetative gonorrheal endocarditis of the pulmonary valve, subacute pericarditis and healed endocarditis of the mitral and tricuspid valves. The diagnosis was made eight weeks after the onset of symptoms.

CASE 7—F. C., a married woman 28 years old, was admitted to the New York Post-Graduate Hospital on Jan 16, 1931. She complained that chills, fever, night sweats and much pain had been present irregularly for two weeks.

TABLE 1—Data on Fourteen Cases of Gonorrheal Sepsis

Case Number	Number Weeks After Onset of Diagnosis Made	History of Heart Disease	Number of Hospital Admissions	Patchiae Present	Gonococcus Complement Fixation	Variation in Murmurs	Spleen Palpable	Pneumonia	Abdominal Pain	Prominent Digestive Disturbance	Streptolysin Titer	History of Gonorrhea	Pleural Effusion	Number of Negative Blood Cultures	Blood Cultures Positive
1	8	None	1	No	Positive	Yes	Yes	Yes	No	Yes	Not done	Yes	No	0	Yes
2	9	Yes	1	Yes	Positive	No	Yes	No	No	No	Positive	Yes	No	0	Yes
3	9	Yes	1	No	Positive	Yes	No	No	Yes	Yes	Not done	No	Yes	3	Yes
4	12	None	3	No	Positive 2 times	Yes	Yes	Yes	Yes	Yes	Negative	Yes	No	5	Yes (post mortem)
5	12	None	2	No	Not done	Yes	Yes	Yes	Yes	Yes	Not done	Yes	No	3	Yes
6	8	None	1	Yes	Doubtful	Yes	Yes	No	No	Yes	Not done	No	No	9	Yes
7	18	None	2	Yes	Not done	Yes	Yes	No	Yes	Yes	Not done	No	No	4	Yes (post mortem)
8	4	Yes	1	No	Not done	Yes	Yes	Yes	No	No	Not done	No	No	2	Yes (post mortem)
9	8	Yes	1	No	Not done	Yes	Yes	Yes	Yes	Yes	Not done	Yes	No	5	Yes
10	4	None	2	No	Positive	Yes	No	No	Yes	Yes	Not done	Yes	No	8	No organism obtained from joint
11	4	None	1	Yes	Not done	Yes	Yes	No	No	Yes	Not done	No	No	1	Yes
12	11	Yes	2	No	Not done	Yes	Yes	Yes	Yes	Yes	Not done	No	Yes	3	Yes
13	3	Yes	1	No	Not done	Yes	No	Yes	Yes	Yes	Not done	No	Yes	2	Yes (post mortem)
14	14	None	2	No	Positive 9 times	Marked	Yes	5 times	Yes	Yes	Not done	Yes	Cloudy	9	No
Average of total	9	6	15	4	7 positive, 7 not done	13	11	8	9	12		7	4	51	12
Percentage of all cases	43			29		93	79	57	64	86		50	29		86

She had been discharged from St Luke's Hospital on Nov 12, 1930, with a questionable diagnosis of acute pyelitis. There was only a slight amount of pus in the urine. The spleen was palpably enlarged. On one occasion, while she was at St Luke's Hospital, it was thought the patient might have pneumonia in view of the presence of fever (103 F) and severe pain in the chest. After leaving this hospital she was never entirely well, at irregular intervals she was harassed by chills and sweats. At the New York Post-Graduate Hospital a few petechiae and varying cardiac murmurs were noted, and splenomegaly was found. There was no evidence of pneumonia. A gonococcus complement fixation test was not done. Nausea and vomiting were prominent symptoms, occasionally there was some abdominal pain. Four blood cultures were sterile. At the time of death, eighteen weeks after the onset of symptoms, a diagnosis of subacute bacterial endocarditis due to *Streptococcus viridans* was made, and it was apparently confirmed at the postmortem examination. The true nature of the condition was discovered only after sections of the heart valves had been studied.

CASE 10—V Y, a woman aged 21, was admitted to the Bellevue Hospital on Sept 14, 1934, she complained of pain, of three days' duration, in the left side of the chest, and in the left knee and wrist. She had been exposed to gonorrhea two months before and had had local treatment during the month preceding admission. There was no history of previous heart disease. There were soft systolic murmurs heard at the apex of the heart and at the base on admission, these did not change. The temperature was 101.5 F on admission. Two days later she had chills and fever. The precordial pain was severe, and a loud pericardial friction rub could be heard. The urethral smear was positive for gonococci. The results of the gonococcus complement fixation test were now positive, although at first negative results had been obtained. Eight blood cultures were sterile. At no time was the spleen palpable. There was no evidence of pneumonia, and there were no petechiae. A diagnosis of gonorrheal pericarditis, arthritis and septicemia was suggested at the onset. Five days after the friction rub had become apparent the patient was given a bout of fever therapy. After six hours at a temperature between 106 and 107 F, she improved. The friction rub almost disappeared, but it reappeared loudly the following day. For the next month she had pains in the joints and pelvis, leukorrhea, low grade fever, precordial pain and nausea. She was then given a second bout of fever therapy, after which her recovery was uneventful. The urethral smears became negative, the friction rub disappeared and the results of gonococcus complement fixation test were negative. At the time of the patient's discharge, seventy-six days after admission, the electrocardiogram was normal, previous tracings had shown changes.

CASE 14—R K, a married man 41 years of age, was admitted to St Luke's Hospital on Dec 13, 1935. In September a low grade fever had developed which continued, on and off, for about six weeks. He had some indigestion and felt as if he had a cold, however, he had no cough, sore throat or pain in the chest and was not ill enough to go to bed. He thought that the drinking of a moderate amount of ale had been the cause of his abdominal distress. This first illness was followed by a period of about six weeks during which he had no complaints and no fever.

On November 1, while he was in Berlin, he became nauseated and vomited just after drinking some rather poor wine. That night his temperature was 102 F. The fever continued irregularly (99 to 102 F) during the next two and

a half weeks During this period he went to Paris, where he was told he had pneumonia and was sent to bed At no time during the illness did he feel particularly sick

By December 1 his temperature was normal and he was allowed to return to the United States While at sea, he drank champagne and afterward he again became nauseated and vomited The next day his temperature was again 102 F, the pulse rate was 100, and the respiration was 26 Physical examination on admission to St Luke's Hospital revealed no other abnormalities, except for a low-pitched nontransmitted systolic murmur at the base of the heart The blood pressure was 120 systolic and 85 diastolic A blood count showed 8,400 leukocytes and 4,900,000 red blood cells The sedimentation rate was 44 mm in one hour There was no urethral discharge, and prostatic examination showed no abnormalities Several teeth appeared to be devitalized The only important particulars in the past history were the facts that during the previous three months the patient had

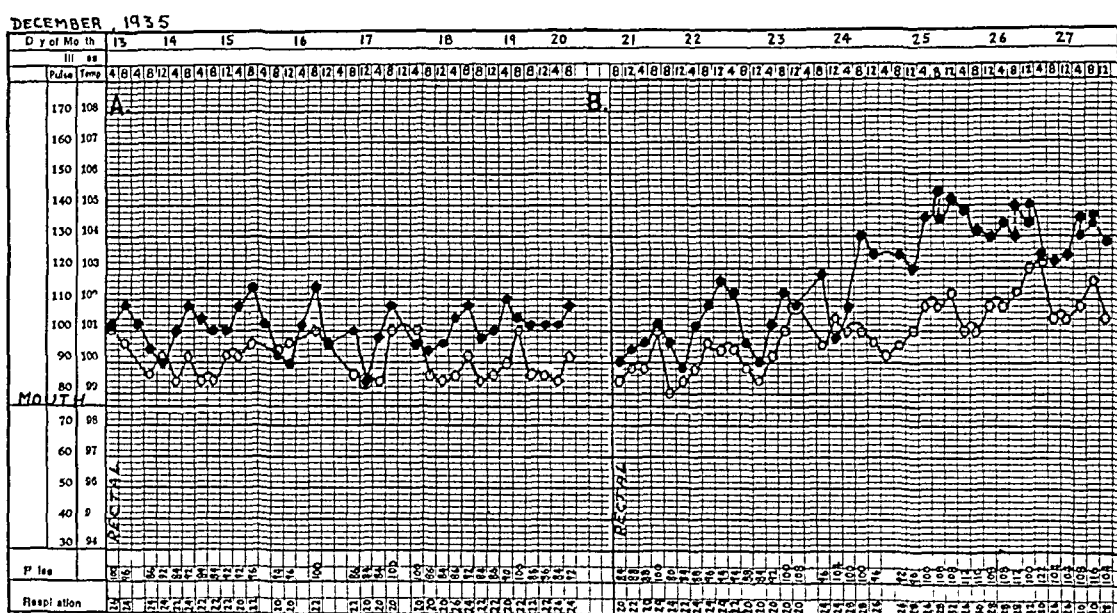


Fig 2 (case 14)—A, temperature (solid circles) and pulse (clear circles) recordings during first eight days in hospital B, temperature (solid circles) and pulse (clear circles) recordings from Dec 21 to 27, 1935

traveled in Italy, Spain, Germany and France and had eaten and drunk in various types of places and that twenty years before he had had a case of severe gonorrhea During the few nights before the onset of the acute illness, he had been on something of a sexual and alcoholic debauch During the first nine days of his stay in the hospital, the temperature varied from 99.4 to 102.2 F Its course in the first eight days is shown in figure 2 A A roentgenogram of the chest on December 14 was negative, agglutination tests for typhoid and undulant fevers were negative, and the blood culture was sterile

The blood count on December 19 showed 5,300,000 red cells and 10,800 leukocytes, of which 22 per cent were lymphocytes, 73 per cent were polymorphonuclear neutrophils, 1 per cent were eosinophils and 5 per cent were monocytes

The complement fixation test for gonococcus was positive on December 13 A gastric analysis on December 21 gave normal results A roentgenogram taken of the sinuses on December 16 showed them to be clear On December 17 a roentgeno-

gram of the teeth showed large abscesses which involved the central and lateral incisors on the upper left side and beginning absorption at the apex of the central incisor on the upper right side and of the central incisor on the lower left side. Gastrointestinal studies on December 16 and 20 gave negative results. Two teeth were extracted on December 19, during the following two days the temperature was slightly lower, but on December 22 it began to rise and by December 25 it had reached 105 F. This phase of the illness is shown in figure 2B.

A roentgenogram of the chest on December 26 showed early consolidation and evidence of fluid at the base of the right lung. A blood culture taken on December 24 was sterile. The sputum at this time was blood streaked and contained many spirochetes and a few pneumococci which could not be typed. The leukocyte count was 23,800 with 86 per cent polymorphonuclear cells. A specimen of urine was normal except for a faint trace of albumin. An electrocardiogram done on December 24 was reported as normal (fig. 3).

During the second week in the hospital the patient was given intradermal injections of a nonspecific milk preparation (aolan) every second day. On December 26, 20 cc of cloudy thick fluid was removed from the chest by aspiration. A

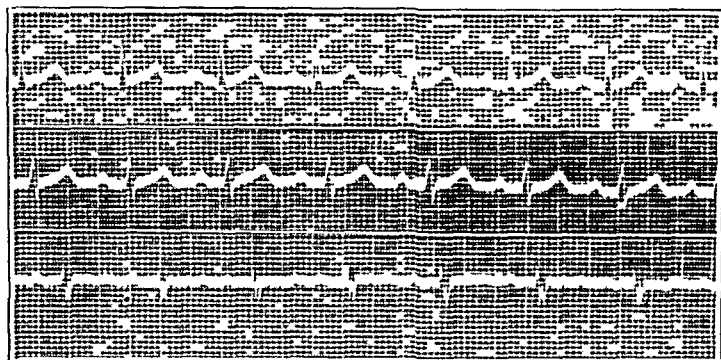


Fig. 3 (case 14) —Electrocardiogram taken on Dec 14, 1935

cell count of the fluid showed 11,750 leukocytes per cubic centimeter, with 88 per cent polymorphonuclears and 12 per cent lymphocytes. No growth was obtained on culture of this fluid. Smear cultures were negative for organisms. Inoculation of guinea pigs gave negative results. No spirochetes could be found. The sputum was negative for tubercle bacilli on December 27.

On December 27, 10 cc of clear fluid was removed from the chest. On Jan 5, 1936, 10 cc of clear straw-colored fluid was removed. By this time the patient, who had been irrational for one week, was again rational, and the temperature had fallen somewhat. During this time he was slightly jaundiced. The urine contained urobilin but no bile. Aspiration was again done on January 8, only 5 cc of blood-tinged, sterile fluid could be obtained. During the next week his condition remained unchanged. On January 15 he again had pneumonia. Pneumococci of type XXVII were cultured from his sputum. No gonococci could be found. His temperature curve during this period is shown in figure 4.

On January 19, at the suggestion of a consultant, a twelfth rib was removed and the diaphragm and liver inspected, without opening the pleural cavity. No pathologic changes were demonstrable. After the operation the fever continued until March 6. The temperature curve for part of the period after operation is shown in figure 4. During this time the patient had two more attacks of

pneumonia In all, he had pneumonia four times Roentgenograms taken on these occasions are shown in figure 5 In table 2 are shown the blood counts and sedimentation rates

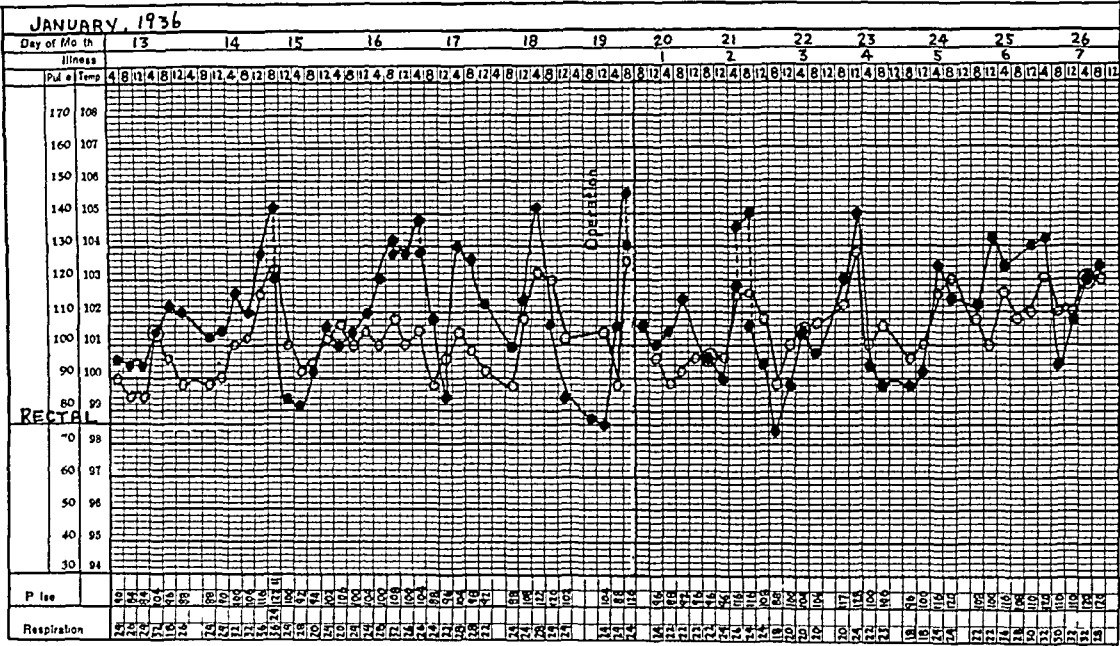


Fig 4 (case 14) —Temperature and pulse recordings, before operation, on Jan 19, 1936, and after operation

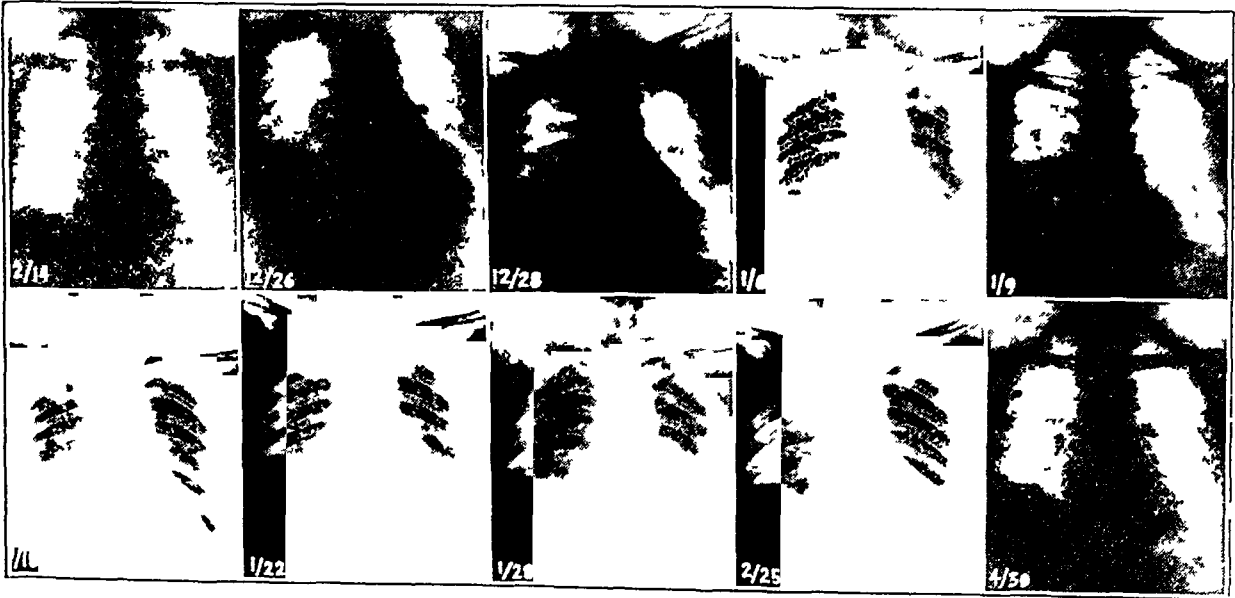


Fig 5 (case 14) —Roentgenograms taken during course of attacks of pneumonia

Nine blood cultures done on various occasions with various kinds of mediums were sterile Miss Margaret Straub, of the New York Post-Graduate Hospital, made some special cultures for gonococci but was unable to obtain any growth

At no time were there any petechiae. The character, intensity and location of the murmur changed from day to day. On three occasions gallop rhythm developed. The electrocardiogram done on March 2 is reproduced in figure 6. In figures 7 and 8 are shown the electrostethographs taken March 10 and April 30, 1936.

The patient was given eleven transfusions of whole blood, but it was not until these were administered every two days that any benefit was noted. He also was given Corbus-Ferry gonococcus filtrate intradermally.

He left the hospital on March 14 in an ambulance, he was not allowed to get up until April 1.

TABLE 2—Laboratory Data for Case 14

Date	Hemo- globin, per Cent	Red Blood Cells	White Blood Cells	Differential			Sedimen- tation Rate	Gono- coccus Comple- ment Fixa- tion
				Neutro- phils	Lympho- cytes	Eosino- phils		
12/13/35	93	4,900,000	8,400	74	21		44	+
12/14/35			12,800	84	16			
12/18/35								+
12/19/35	93	5,300,000	10,800	72	27	1		
12/24/35	100	4,100,000	23,800	84	14	2		
1/11/36	66	3,800,000	11,300	86	14			
1/20/36	74	4,670,000	18,800	60	40			
1/28/36	81	4,620,000	17,900	92	8			
2/ 5/36	79	4,220,000						
2/13/36								
2/25/36	57	5,500,000	22,800	78	22			
3/ 6/36	64	6,050,000	11,400	76	24			
3/ 9/36	76							
3/11/36	76	5,400,000	9,400	76	24			
3/13/36							40	+
3/21/36	96	5,100,000					31	
3/24/36								+
3/31/36		5,100,000	19,800					+
4/ 4/36							60	
4/ 9/36								+
4/18/36							30	
5/ 2/36							12	
5/28/36								+
6/ 1/36							12	+
7/ 8/36		6,500,000	12,000				9	
8/14/36	118	5,500,000	9,400	43	57		8	+

On April 12 his temperature began to rise again, and he was given another transfusion. He was allowed to walk on May 15. By June 1 he was feeling well and had gained about 20 pounds (9 Kg). The pulse rate averaged 84, and the diastolic murmur had disappeared. The sedimentation rate was normal.

Comment—This case is reported in some detail because of certain unusual features and because of the recovery in what seemed to be, but was not entirely proved to be, a case of gonococcic endocarditis. Friedberg⁷ stated that the symptoms which are specifically referable to endocardial involvement consist essentially of embolic phenomena and alteration in heart sounds.

A case reported by Perry¹⁰ in 1930 is so similar to this case that a brief summary of it seems fitting. His patient recovered after seventy-

¹⁰ Perry, M. W. Gonorrheal Endocarditis with Recovery. Case Report, *Am J M Sc* 179 599, 1930.

three days in the hospital, during which period he had pneumonia three times (pulmonary emboli). There was a systolic murmur, which later became diastolic, over the area of the pulmonary valve. There were no petechiae. The patient's feeling of well-being was out of proportion to his symptoms. He received fourteen blood transfusions (each of 250 cc of citrated blood) and 150 cc of immune serum. He was also

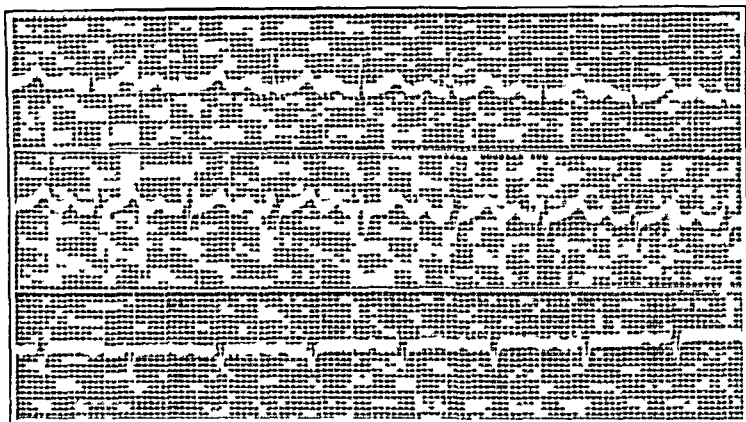


Fig 6 (case 14) —Electrocardiogram taken on March 2, 1936

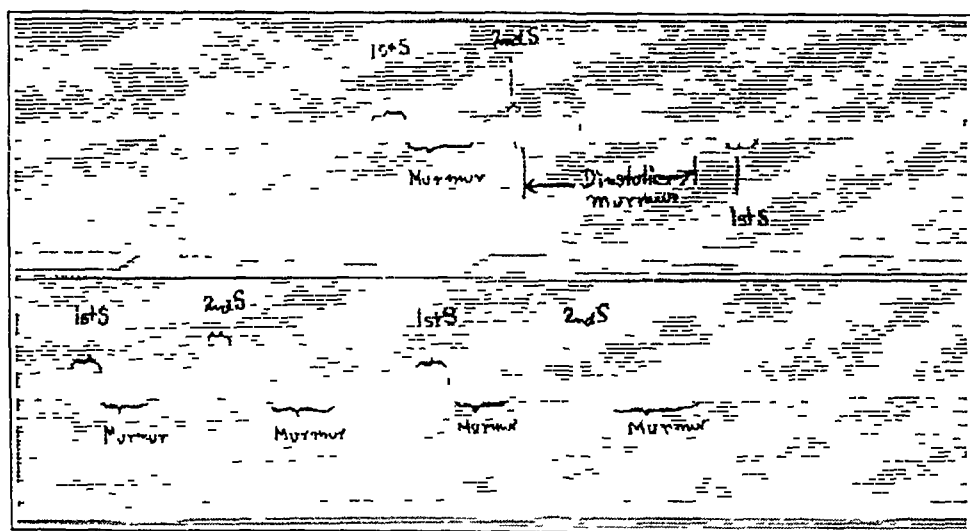


Fig 7 (case 14) —Electrostethograph taken on March 10, 1936

given gonococcus vaccine. In this case, however, gonococci were found both in the urethral smear and, finally, after repeated cultures, in the blood stream. In my case, I was not able to obtain the organism. In 1933 Perry¹¹ gave a follow-up report on his case and noted that the patient seemed well, and the electrocardiogram showed no abnormalities. The diastolic murmur, however, still persisted.

11 Perry, M. W. Further Note on Case of Gonorrheal Endocarditis with Recovery, *Am J M Sc* 185:394, 1933.

Since I was unable to demonstrate the gonococcus in my case, it might be argued that the diagnosis was not correct, but the following points appear to substantiate it

1 The gonococcus complement fixation test was positive nine times. There are many who will say that this test has been largely discredited, for example, the New York Board of Health stopped using it as a routine measure. This opinion, however, is fast giving way, and the test, as now done, is accurate to a fairly high degree. Recently Barringer expressed the view that the test is one of the most valuable in medicine.¹²

2 There were no petechiae

3 The heart murmurs varied from day to day

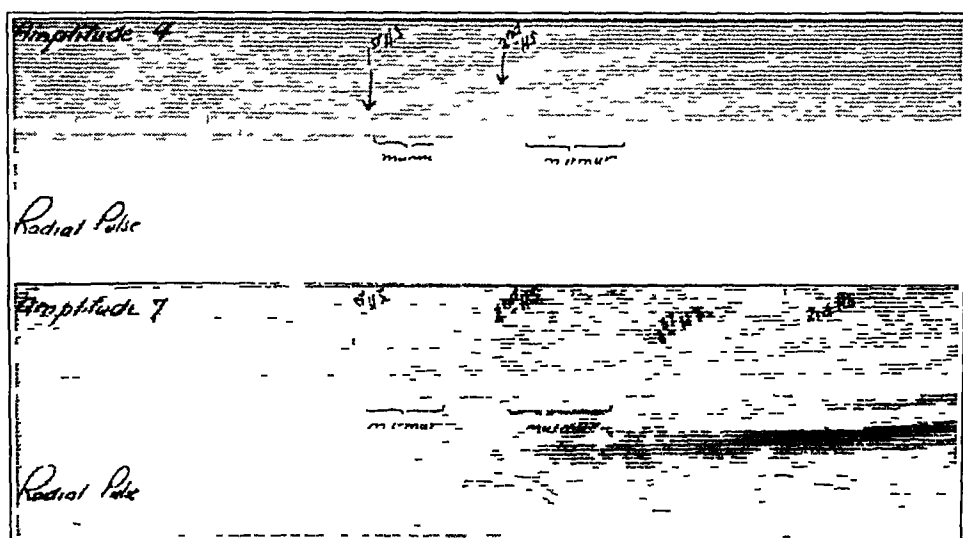


Fig 8 (case 14) —Electrostethograph taken on April 30, 1936

4 There was no change in conduction time of the heart, such as would be expected in a rheumatic infection. Levy and Turner¹³ stated that disturbances in auriculoventricular conduction time are found more often in rheumatic fever than in any other disease. In endocarditis due to the gamma nonhemolytic streptococcus and in subacute bacterial endocarditis due to the viridans (alpha) electrocardiographic changes are uncommon. Sabathie,¹⁴ however, has stated that one type of gonorrheal endocarditis, which he termed "la myo-endocardite gonococcique,"

12 Barringer, E. D. Complement Fixation Test. A Diagnostic Aid in the Control of Gonorrhea, New York State J. Med. **38** 699, 1938.

13 Levy, R. L., and Turner, K. B. Impaired Auriculoventricular Conduction in Rheumatic Fever, Arch. Int. Med. **43** 267 (Feb.) 1929.

14 Sabathie, L. G. La myo-endocardite gonococcique. Sa pathogenie, Bull. et mem. Soc. med. d. hop. de Paris **51** 610, 1935.

is associated with electrocardiographic changes, and that these changes are due to involvement of the intraventricular bundle. In this type there are no embolic phenomena, and valvular involvement is late and not as significant.

5 After bouts of pneumonia, in which there had been sustained fever, there would be a period during which the patient had a comparatively low temperature, which probably indicated that the invading organism was sensitive to heat, such sensitivity is characteristic of the gonococcus. Some writers invoke the theory that the extreme thermolability of the gonococcus is responsible for cases of gonorrheal sepsis in which there is spontaneous remission. For this reason, in this instance it had been suggested that the patient be blanketed when his temperature reached 106 F, and that an attempt be made to keep his temperature at this level for several hours in an effort to kill the gonococci. However, I was diffident and this measure was not tried.

6 The cloudy fluid removed from the cavity in the chest was apparently sterile, similar observations are made in gonorrheal pleurisy.¹⁵

7 The history included a severe attack of gonorrhea twenty years before and recent alcoholic and sexual excess.

8 Recovery followed multiple blood transfusions and the administration of Coibus-Ferry filtrate.

9 The patient had five attacks of pneumonia which was probably embolic.

10 Jaundice was present, however, it was most probably due to hemolysis.^{15a}

11 The spleen was palpable.

12 Gallop rhythm was noted on three occasions.

13 The patient suffered from such severe abdominal pain (probably embolic in character) that an exploratory operation was performed.

Ross and Greaves¹⁶ reported 2 cases of gonorrheal endocarditis proved at autopsy. In 1 there was an embolic pneumonia. In the other the diagnosis was not made for some time after the onset of the disease, the appendix, which was removed because of abdominal pain, tenderness and rigidity, was normal. The authors stated the belief that the abdominal symptoms had been embolic in origin. No petechiae were seen in either case.

15 Pratsicas, A. Contribution a l'etude des manifestations viscerales de la gonococcie (endocardite, pneumonie), *Paris med* 1 521, 1928.

15a Tice, F., Friedenwald, J., and Warren, L. F. *The Practice of Medicine*, Hagerstown, Md. W. F. Prior Company, Inc., 1932.

16 Ross, C. W., and Greaves, F. C. Gonococcic and Meningococcic Endocarditis with Report of Three Cases, *U. S. Nav. M. Bull.* 33 179, 1935.

14 There was evidence of renal infarct (blood and casts in the urine) In this connection it is interesting to note that in this disease death is often of renal origin¹⁷

COMMENT

In certain cases, such as those in which the acute disease follows trauma to the urethra in the course of treatment of acute gonorrhea, the diagnosis is simple It is not relative to this type of case that this paper is written However, it seems fitting to call attention to such cases, because if my findings are kept in mind an earlier diagnosis may be made, which will prevent useless major operations and explorations of the chest and will hasten the patient's recovery Moreover, it would appear that if sulfanilamide or fever therapy could be used early in the disease the mortality could be much reduced

TABLE 3—Data for Cases Recorded at Mount Sinai Hospital

Case No	No Weeks After Onset Before Diagnosis	History of Heart Disease	Admitted 2 or More Hospitals	Petechiae Present	Gonococcus Complement Fixation	Variation in Murmurs	Spleen Palpable	Pneumonia
15	4	No	No	Yes	Negative	Yes	Yes	No
16	32	No	No	Yes	Not done	Yes	No	No
17	1½	No	No	Yes	Yes	Yes	Yes	No
18	5	No	No	Yes	Not done	Yes	Yes	Yes(1)*
19	8	No	No	No	Yes	Yes	Yes	No
20	14	No	No	Yes	Yes	Yes	Yes	No
21	2½	Yes	No	Yes	Negative	Yes	Yes	Yes (1)
22	8	Yes	No	Yes	Not done	Yes	No	Yes (1)

* The patient had one attack

The cases recorded at Mount Sinai Hospital are summarized in table 3 Several of these cases have been reported by Newman³ and by Friedberg⁷ Case 20, in which recovery took place, was reported in detail, the final diagnosis was gonorrheal endocarditis

Williams¹⁷ has recently reported 2 cases of gonorrheal endocarditis which are of interest In the first case there was no previous history of gonorrhea, and the diagnosis was not made until the patient had been acutely ill for five weeks The first three blood cultures were negative, the fourth, fifth and sixth, done over a period of fifteen days, were positive Although this patient had serious renal and hepatic disease, he was placed in the Kettering hyperthermia After one fever treatment his blood became sterile Unfortunately, the patient became anuric, although he seemed to bear the treatment well He was given a second fever treatment, which was well tolerated The next day he died of renal insufficiency It may be stressed that gonorrheal sepsis

17 Williams, R H Gonococcal Endocarditis Treated with Artificial Fever (Kettering Hyperthermia), *Ann Int Med* 10 1766, 1937

can, of itself, produce marked renal damage and cause uremia. The interesting and important features are that after the fever treatment the gonococcemia disappeared ante mortem and that the blood and the gonococcic vegetation in the heart were sterile on postmortem examination. The possibility that fever treatment may have intensified the manifestations of uremic intoxication was considered, but the necropsy threw no light on this. The second case reported by Williams was one of gonorrheal septicemia which developed in a man aged 46 twenty years after an attack of gonorrheal urethritis. The patient had been told eight years before that he had a "slightly leaking heart valve." It was unusual that one of his first symptoms was the appearance of petechiae. He also had a mitral murmur which changed in quality and in intensity. There were slight electrocardiographic changes, which were interpreted as being due probably to transient myocardial disease (questionable embolism). Four blood cultures were negative. Gonococci could not be demonstrated in the urethral or prostatic secretion. Two weeks after admission, or five weeks after the onset of symptoms, the right ankle became swollen, painful and tender, pus aspirated from it contained gonococci. Twenty-four days after admission it was decided that the patient had gonorrheal endocarditis, and he was given three treatments in the Kettering hyperthermia. The temperature was maintained between 105 and 106 F for five hours, and on one occasion it rose to 108.2. After the first treatment his temperature returned to normal, and it remained practically normal thereafter. The mitral murmur became less harsh. Six months later, the results of the follow-up examination were essentially normal except that a faint systolic murmur was heard at the area of the mitral valve. The sudden onset of this patient's illness, with a chill and high fever, the presence of numerous large petechiae with areas of central necrosis, the high, septic fever with occasional chills, the transient multiple arthritis, with subsequent development of acute purulent monarticular arthritis from which gonococci were obtained, the presence of transient electrocardiographic alterations indicating acute changes in the myocardium, and the change in character of the apical murmur constitute convincing evidence of severe (metastatic) gonococcic infection and they strongly suggest that gonococcic endocarditis was present.

In a recent article, Williams² reported 12 cases of fatal gonorrheal endocarditis seen at the Vanderbilt University Hospital. He emphasized the importance of the disease, and stated that it is not rare, since it was present in 26 per cent of the patients with bacterial endocarditis (acute and chronic) at the Vanderbilt University Hospital. He stated that careful observation and thorough laboratory examinations will lead to a correct diagnosis and that although the prognosis is grave the use of the Kettering hyperthermia and sulfanilamide offers some hope.

Thayer¹ stated that gonorrhea is an infection which is focal at first but which spreads not only by direct extension but also, and not infrequently, through the blood stream. In the latter case there is a general septicemia associated with a variety of metastases—notably arthritis, synovitis and myositis and not infrequently endocarditis, myocarditis or pericarditis. Of 176 instances of acute endocarditis of determined origin, 11.3 per cent were gonococcal. Thayer stated that “gonorrheal cardiac infections as a whole are by no means very unusual.” In his series, involvement of the pulmonary orifice was fairly common, but the aortic valves were most commonly involved. The duration of the disease was usually from four to nine weeks.

In 1933 the Welfare Council of the Works Progress Administration made a survey of the diagnoses of all the patients admitted to New York hospitals during that year. There were 567,000 hospital discharge schedules that year. In only 4 of these was a diagnosis of gonorrheal endocarditis recorded, although in 4,540 schedules the diagnosis of gonorrhea of various types was given.

White¹⁸ has stated that gonococcus, *Streptococcus haemolyticus*, the pneumococcus and *Staphylococcus aureus*, in equal frequency, are the organisms responsible in nearly 100 per cent of the cases for acute bacterial endocarditis. He also stated that gonorrheal endocarditis is almost invariably fatal.

DIAGNOSIS

In order to furnish assistance in establishing the diagnoses during the delay incident to obtaining positive blood cultures, certain diagnostic points have been gleaned from the cases here reported and from the literature. These are given in the following list:

- 1 A history of gonorrhea may be noted.
- 2 Chills and septic temperature may be present. They are less severe if gonococcemia is present without endocarditis.
- 3 Frequently the temperature curve shows two peaks of fever in one day.
- 4 After high or sustained fever, such as occurs in embolic pneumonia, the temperature is apt to become nearly normal.
- 5 The gonococcus complement fixation test, if repeatedly positive, is of great diagnostic value.
- 6 A positive blood culture is often difficult to obtain. The organism grows more readily in venous blood, hence there is better chance for growth if the culture is kept in an atmosphere of carbon dioxide and if the blood sample is obtained from an artery before the blood has traversed the whole arterial tree.
- 7 The right side of the heart is more frequently involved than the left, but the site of involvement may vary with the point of origin of the infection.
- 8 If pneumonia, which is frequently present because of the occurrence of embolism, is present it is more difficult to obtain a positive blood culture because the capacity of the lungs to act as a filter is increased.

18 White, P. D. Heart Disease, New York, The Macmillan Company, 1934.

9 Sudden abdominal pain is a frequent embolic phenomenon In 2 of the cases here reported the diagnosis of an acute condition in the abdomen was made, and in 1 of these cases an exploratory operation was done

10 Renal irritation is often noted, blood, pus and casts may be found in the urine, and death is frequently due to uremia

11 Cutaneous lesions are sometimes seen, the characteristic lesion is an erythematous macule that acquires a central vesicle or pustule This is usually seen in gonococcemia without endocarditis

12 Varying roughened cardiac murmurs—usually diastolic—may be present

13 Petechiae are not as common as in other types of bacterial endocarditis

14 The spleen is more apt to be enlarged than in other types of bacterial endocarditis

15 The electrocardiogram is usually normal, unless pericarditis or abscess is present

16 The antistreptolysin titer and cutaneous tests with nucleoprotein are negative unless the patient has had rheumatic fever

17 Arthritis is present in about 50 per cent of the cases

18 Jaundice is frequently present

19 The average white cell count is higher than in other types of endocarditis

20 The symptoms fail to respond to the administration of salicylates

21 Exacerbation of chills and temperature occurs following prostatic massage

RESUME

From a study of the data collected in this paper, certain points stand out (1) the difficulty in establishing a definite diagnosis, which is often not made until after death, (2) the frequent occurrence of pneumonia, (3) the infrequency of petechiae and the peculiarity of the cutaneous lesion, (4) the difficulty attendant on obtaining a positive blood culture, and (5) the fact that recovery is possible

These points will be discussed briefly in order

Difficulty in Diagnosis—The condition is rarely thought of unless there is a recent history of gonorrhea A case observed recently in St Luke's Hospital illustrates this point

CASE 23—The patient, a man 72 years old, had had gonorrhea forty years before He was admitted to the hospital on April 26, 1938, with a history of having had fever (temperature as high as 106.5 F) and chills, off and on, for four weeks Several joints had been swollen and hot, the involvement was migratory His condition was diagnosed as acute rheumatic fever He did not respond to the administration of salicylates A section of the temperature curve while he was at the hospital is given in figure 9 The white cell count was 52,000 on one occasion No murmurs were heard in his heart On one occasion, after his temperature had reached 106.6 F, he had a transient hemiplegia On several occasions he had numerous rales at the bases of the lungs At one time he was given prostatic massage, he then had a severe chill and his temperature went to 106 F The gonococcus complement fixation test was positive, with both antigens, on two occasions Four blood cultures remained sterile His right

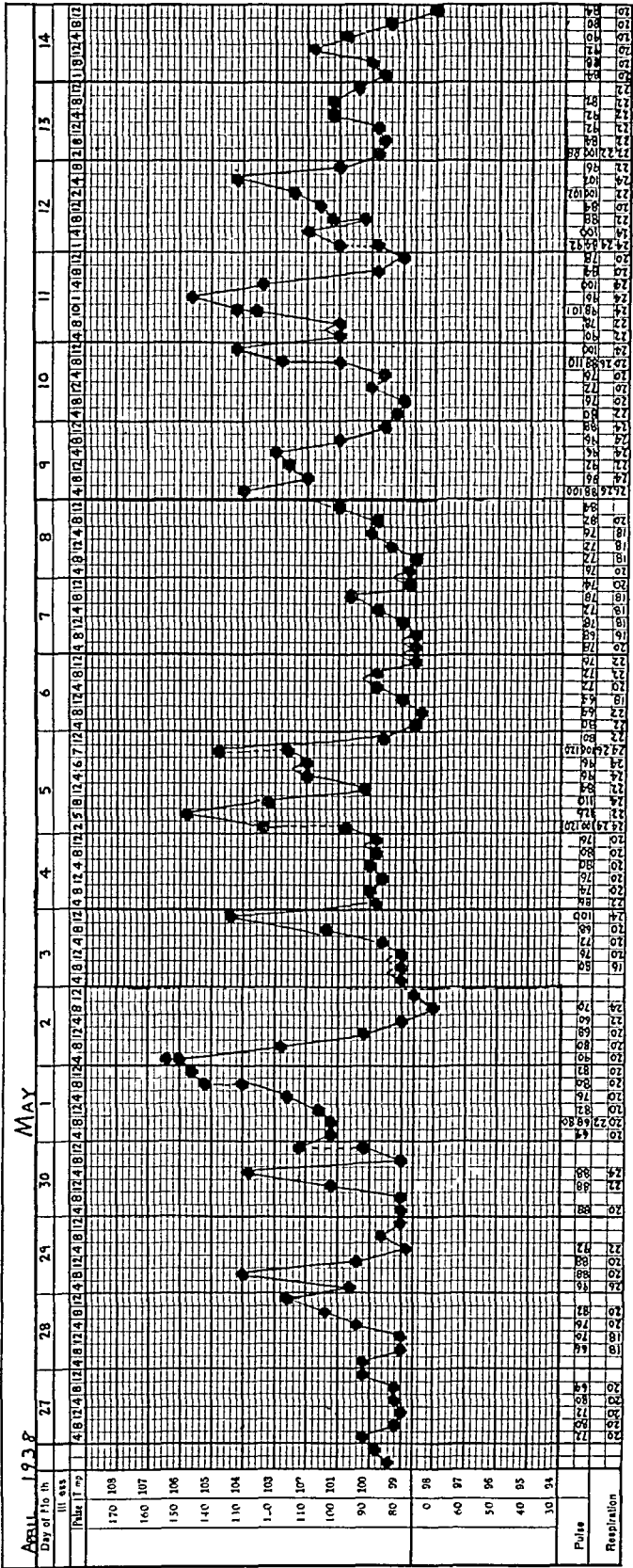


Fig 9 (case 23) —Section of temperature curve during the patient's stay in the hospital

knee and wrist had the typical appearance of a joint with a gonorrheal infection. On May 15 the administration of sulfanilamide was begun. On May 17 he was given a transfusion of 500 cc of whole blood. By May 30 his temperature had been practically normal for ten days, and he was allowed to sit up. Pain and stiffness in the right knee were his only complaints at that time. He was discharged from the hospital on June 16. When last seen he had made a complete recovery and had returned to work.

Frequent Occurrence of Pneumonia—According to Schottmueller¹⁹ the metastasizing tendencies of bacteria differ. Anaerobic streptococci and Welch bacilli have slight tendency to metastasize, although they circulate freely in the blood. Staphylococci metastasize in most instances. Gonococci produce mostly valvular, articular and cutaneous foci, while meningococci produce, almost exclusively, cardiac, meningeal and cutaneous lesions. Gonococci, pneumococci and meningococci tend to settle especially on the valves of the right side of the heart, indicating, perhaps, that conditions for the multiplication of these organisms are better in venous blood, hence, also, the frequency with which pulmonary infarcts develop. It is estimated that in about 12 per cent of the cases of sepsis the infection is in the form of endocarditis, which is practically always fatal, in about 60 per cent of the cases it is in the form of thrombophlebitis, which has a mortality of 70 per cent, and in about 10 per cent of the cases it is in the form of lymphangitis, with a mortality of 50 per cent.

If bacteria from a thrombophlebitis or some other focus float into the blood stream, they will be arrested in the lungs in either a large branch of the pulmonary artery or in the capillary sieve, depending on their size. There are three possible ways by which they may reach the greater circulation. 1. Bacteria may pass through the open foramen ovale or through the interventricular septum. 2. They may pass through the filter formed by the pulmonary capillaries. (This is possible because blood corpuscles of large size can pass the capillary filter.) However, the sensitized pulmonary capillary bed has tremendous phagocytic power and filters out extraordinary numbers of bacteria. (I am reminded of a case seen by Keil,²⁰ in which no petechiae developed until just before death, when they appeared in great numbers. This sudden appearance was attributed to failure of the pneumonic lung to act as a filter.) 3. A new focus of infection in the pulmonary circulation receives bacteria-containing plugs which form infected infarcts and suppurating metastases and such a metastasis may then become connected with the pulmonary vein in the sense of a thrombophlebitis and so bacteria reach the greater circulation through infected thrombotic particles. Therefore, one must assume the existence of a new septic focus.

19 Schottmueller H. Treatment of Syphilis of Aorta, Am J Syph 9 1 1925.

20 Keil, H. Personal communication to the author.

In the lung a primary septic focus may develop as, for example, in grip Fraenkel²¹ and others have demonstrated the dissolution of foci into the arteries and veins of the lungs Wohlwill²² demonstrated in 21 of 24 cases of metastasizing sepsis the presence of a secondary septic focus in the anatomic area under discussion This is a high percentage not even surpassed by the demonstration of vascular foci in the form of caseous endangitis in miliary tuberculosis, in which the pathologic process is essentially the same As thrombophlebitic sepsis occurs principally in the tributary area of the vena cava, one is dealing mostly with the existence of secondary septic foci in the lungs, namely, in pulmonary veins Accordingly, blood coming from the infectious focus should contain the greatest numbers of bacteria If the arterial blood contains more bacteria than the venous blood, a secondary septic focus has arisen either in the lungs or in the heart It therefore seems advisable to make cultures from the arterial circulation in the greater hope of obtaining one positive for gonococci Nathan²³ in 28 of 31 cases of metastasizing sepsis in which death occurred noted the presence of thrombophlebitis of the pulmonary vein Before 1932 this condition was not sought for, as the bacteremia was explained on the basis of the passage of bacteria through the pulmonary capillaries This theory, of course, rejects the assumption that multiplication of bacteria takes place in the circulating blood

Nathan²³ reported a case of sepsis secondary to the introduction of a bougie into the urethra in a young man treated for gonorrhea A prostatic abscess developed, and there was infiltration in both lungs, the clinical picture was that of metastatic sepsis with fever Autopsy showed thrombophlebitis of the venous plexus of the prostate and the development of pulmonary abscesses from septic pulmonary emboli, in one of these abscesses there was a thrombophlebitis of a larger vein, which constituted the focus through which the infection reached the general circulation

In 1 patient in my series there was apparently a septic infarct or an embolic abscess near the pleura which ruptured through the latter, producing an empyema Multiple pulmonary infarcts occurred from a right-sided mural thrombus A later deeper infarct was accompanied by a serous effusion

Infrequency of Petechiae and the Peculiarity of the Cutaneous Lesion—Petechiae are probably less frequent in gonococcemia than in other types of sepsis, because, as stated previously, the organism usually fails

21 Fraenkel E Ueber postanginose Pyämie, Virchows Arch f path Anat **254** 639, 1925, Deutsche med Wchnschr **53** 93, 1926

22 Wohlwill, F Pathologisch-anatomische Beiträge zum Problem der Sepsis, Arch de pat **7** 157, 1935

23 Nathan, H Neuere Gesichtspunkte zur Sepsisfrage, Chirurg **4** 369, 1932

to get through the pulmonary filter. Other cutaneous lesions are more often seen in gonococcemia. They have been well described by Keil²⁴ in an article and in a personal communication.²⁰

Of the various types of eruption, some are distinctive, but others are banal and therefore are of little help in formulating a diagnosis. As gonococcic endocarditis occurs in but a small percentage of patients afflicted with this form of bacteremia, the cutaneous lesions, for the most part, indicate an infection of the blood stream in the absence of a complicating endocarditis. The recognition of these eruptions is of diagnostic and prognostic importance.

The most distinctive cutaneous lesions in gonococcic bacteremia are

- 1 Keratoderma blenorrhagicum and variants. This lesion indicates the presence of bacteremia. So far as I can gather, there are no cases of proved gonococcic endocarditis in which this dermatosis has been observed.

- 2 Hemorrhagic vesiculopustular and bullous lesions of the skin. The clinical picture is somewhat analogous to that seen in keratoderma blenorrhagicum. However, it seems easier to isolate the organism in these cases. In none of these cases has there been proof of an associated endocarditis. In Massini's²⁵ case, an isolated one to be sure, postmortem examination showed the heart to be free of abnormalities.

- 3 Lesions resembling Osler's nodes. The presence of Osler's nodes is uncommon in gonococcic subacute bacterial endocarditis. Occasionally one sees somewhat similar lesions in cases in which there is but little evidence of endocarditis and in which complete recovery seems to ensue. The status of this manifestation is still uncertain, and continued observations appear to be essential before more definite conclusions can be reached in regard to the significance of this lesion.

- 4 Purpura. This lesion, is occasionally seen, it will always be necessary to eliminate the possibility of a coincidental renal insufficiency or of the presence of jaundice as the cause.

- 5 Petechial manifestations—localized or diffuse. These may occur in the absence of a complicating endocarditis. Petechiae found as small lesions on the chest, abdomen, conjunctiva and mouth are of greater significance when they show white or pale centers and occur in crops. In such instances they generally indicate the presence of endocarditis. Special significance must be given to cases of right-sided endocarditis due to gonococci characterized by many episodes of pulmonary disease and by petechial lesions that appear late in the course or terminally. I have

²⁴ Keil H. A Type of Gonococcal Bacteraemia with Characteristic Hemorrhagic Vesiculo-Pustular and Bullous Skin Lesions, *Quart J Med* 7 1 1938

²⁵ Massini, R. Ueber Gonokokkensepsis, gonorrhoeisches Exanthem gonorrhoeisches Phlebitis. *Ztschr f klin Med* 83 1 1916

seen 1 such case. The clinical picture is essentially the same as in cases of subacute bacterial endocarditis of the right side of the heart due to *Str. viridans*.

Difficulty Attendant on Obtaining a Positive Blood Culture—There are three factors in this difficulty: (a) The gonococcus is easily killed; (b) The cultures should be placed under carbon dioxide so that they will not take up oxygen from the air; (c) Few organisms reach the brachial veins, especially when pneumonia is present to increase the capacity of the lung as a filter (petechiae and pneumonia rarely occur at the same time).

Possibility of Recovery—Three cases of gonorrheal septicemia with endocarditis in which recovery took place have been reported. One of these was a case of pericarditis. In another, the gonococcus was never

TABLE 4—Data on Three Cases of Gonococcic Endocarditis with Recovery

Observer	Blood Culture	Pneumonia	Duration, Weeks	Treatment	Organism Obtained from Local Lesion	History of Gonorrhea
Perry ¹⁰ (1928)	Positive	3 times	15	15 transfusions gonococcus vaccine	Yes, urethral smear	Yes
Williams ¹⁷ (1937)	Negative	No	10	Kettering hypertherm, temperature to 108 F	Yes, knee joint	Yes, 20 yr before
Garlock, J. A. M. A. 97-999 (Oct 3) 1931	Positive	No	12	Salpingectomy, 5 transfusions	Yes, cervical smear	No

obtained. There, however, seems to be little doubt of the diagnoses in the third case.

Certain essential features of these 3 cases and the treatment used are presented in table 4.

TREATMENT

The treatment and the important diagnostic points in the 3 cases of my series in which the patients recovered are given in table 5. The case of probable gonococcemia (case 23) seen recently at St. Luke's Hospital is not included in this table.

In summary, accepted forms of treatment would seem to be: (1) administration of sulfanilamide, up to 150 grains (9.72 Gm.) daily, (2) artificial fever induced by the Kettering hypertherm, (3) blanketting the patient, thus utilizing the patient's body heat to maintain a fever, (4) multiple blood transfusions, and (5) surgical removal of any focus of infection (frequently never found even at an autopsy).

That sulfanilamide must be given with great caution is illustrated by its effects in a case of subacute bacterial endocarditis recently at

TABLE 5—Data for Three Cases with Recovery in Present Series

Case No.	Electrocardiogram	History of Gonorrhea	Gonococcus Isolated	Treatment	No Weeks After Onset Before Diagnosis	Duration of Disease	No of Positive Blood Cultures	History of Previous Heart Disease	Cardiac Involvement	Gonococcus Complement Fixation	Temperature
10	Isolated ST segment and diphasic P wave in leads I and II, normal after recovery	2 mo before	Yes, urethral smear; patient had salpingitis and articular involvement	Kidney hyperthermia	1	14 wk	None	8	Systolic murmur at base and apex, loud pericardial friction rub	Positive, negative after recovery	Septic, to 107°, recovery following highest sustained temperature
11	No change	25 yr before	No	Multiple transfusions in conjunction with the patient's high temperature	11	9 mo	None	9	Systolic and diastolic murmurs at apex, systolic murmur at base varied from day to day, gallop rhythm	Positive	Septic to 106°, recovery following highest sustained temperature
20	No change	4 mo before	Yes, from the blood	1 transfusion	14	18 wk	3	1	Systolic murmur at apex, diastolic murmur at the base	Positive	Septic, to 107°, recovery following highest sustained temperature

St Luke's Hospital The patient was given from 80 to 200 grains (5.17 to 12.96 Gm) daily for three weeks His blood counts are given in table 6 The administration of the drug was stopped some time before the lowest count was obtained

TABLE 6—*Effect of Sulfanilamide on Blood Count*

Date	Hemoglobin, per Cent	Red Blood Cells	White Blood Cells	Neutro phils per Cent	Lympho cytes per Cent	Large Mononuclear Cells and Transition Forms, per Cent
3/17/38	80	5,160,000	25,500	88	9	3
4/ 7/38	50	3,100,000	11,700	80	16	4
4/ 9/38	53	3,800,000	11,200	89	10	1
4/11/38	52	3,850,000	4,600	52	18	
4/13/38	45	3,100,000	800	4	96	
4/15/38	60	3,300,000	700	2	98	
4/17/38	50	3,250,000	350		100	
4/18/38	51	3,400,000	200		100	

CONCLUSIONS

Gonorrheal endocarditis is a fairly common disease The diagnosis can and should be made early so that proper treatment may be instituted Since a positive blood culture is frequently hard to obtain and is not the only diagnostic criterion, it is not absolutely necessary, and it may be dangerous to delay the diagnosis for lack of this one determination The high percentage of diagnoses made at autopsy bears mute testimony to this The high mortality should, in the future, be curtailed, and the majority of the patients should recover

Dr Edgar Mayer and Dr Harry Keil read this paper and offered suggestions

BACTERIAL ENDOCARDITIS AND SYPHILIS OF THE AORTIC VALVE

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It has long been known that bacterial endocarditis usually develops on valves which have been the seat of a preexisting deformity. Particularly is this true of the subacute type of the disease. Moreover, it has been well recognized that in the vast majority of instances the antecedent defect arises as a sequel of rheumatic fever and that less commonly it is the result of a congenital malformation. Yet no specific reference pertaining to the coexistence of bacterial endocarditis and syphilitic involvement of the aortic valve appeared in the literature until 1917, when Libman¹ remarked on the infrequency with which subacute bacterial endocarditis attacks valves previously damaged by syphilis. He reiterated this observation in 1918,² in 1920³ and again in 1923,⁴ pointing out in striking contrast the comparably high incidence of both rheumatic and syphilitic aortic valvular disease per se. Unfortunately, the number of such cases observed by Libman is not recorded in his papers. Since then numerous publications have appeared indicating the rarity of this combination, but, when subjected to critical analysis, only a few of the reported cases may be regarded as proved.

It is therefore appropriate at this time to present a critical review of the literature and to add 7 proved instances of syphilitic aortic valvular disease complicated by acute or subacute bacterial endocarditis, thus directing further attention to the coexistence of these lesions.

DIAGNOSTIC CRITERIA

That there may be no misinterpretation of what has been accepted as pathologic evidence of syphilitic valvular disease and of bacterial endo-

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1 Libman, E. Affections of the Valves of the Heart, *M Clin North America* 1 573 (Nov) 1917

2 Libman, E. Streptococcic and Influenzal Endocarditis, *M Clin North America* 2 117 (July) 1918

3 Libman, E. Discussion on Clinical Significance and Course of Subacute Bacterial Endocarditis, *Brit M J* 2 304 (Aug 28) 1920

4 Libman, E. Characterization of Various Forms of Endocarditis, *J A M A* 80 813 (March 24) 1923

carditis respectively, a few prefatory remarks seem apposite. In accord with the criteria of Cabot,⁵ Karsner,⁶ Saphir and Scott⁷ and others, the following gross anatomic changes were regarded in this study as pathognomonic of syphilis of the aortic valve: (1) widening of the commissures separating the aortic leaflets, (2) fusion of the lateral portions of the cusps to the aortic wall of the sinus of Valsalva and (3) wrinkling and puckering of the aortic intima immediately above the aortic valve.

The anatomic differentiation between the acute and subacute forms of bacterial endocarditis is notably difficult in some instances. For the purpose of this study, however, the criteria laid down by Buchbinder and Saphir⁸ for the diagnosis of subacute bacterial endocarditis were accepted as adequate. Those authors expressed the opinion that the presence of the majority of the following anatomic changes was in favor of this diagnosis: (1) large vegetations, (2) evidence of old valvular lesions (rheumatic, nonspecific, syphilitic or congenital malformations), (3) involvement of the adjacent mural, auricular and ventricular endocardium and chordae tendineae, (4) minute ulcerations of the leaflets of the valve and (5) presence of cocci in chains in sections of the vegetations. Clinically, conditions lasting for six weeks or longer were regarded as of the subacute type.

REVIEW OF THE LITERATURE

Kastner⁹ (1918) recorded a single instance of a 32 year old woman with a history of "rheumatic" pains in the left hip for one and a half years. The clinical signs of endocarditis lenta, aortic insufficiency and tertiary syphilis were elicited. The blood culture revealed *Streptococcus viridans*, and the Wassermann reaction of the blood was positive. At necropsy, ulcerative endocarditis of the aortic valve, syphilitic aortitis and aortic insufficiency were observed. The aortic cusps were thickened and shortened, but no description of the commissures is included in the protocol. Although several subsequent authors have accepted this case as an undisputed instance of syphilitic aortic insufficiency, on the basis

5 Cabot, R. C. *Facts on the Heart*, Philadelphia, W. B. Saunders Company, 1926.

6 Karsner, H. T. *The Pathology of Endocarditis. A Summary Review*, J. A. M. A. **96** 411 (Feb. 7) 1931.

7 Saphir, O., and Scott, R. W. *The Involvement of the Aortic Valve in Syphilitic Aortitis*, Am. J. Path. **3** 527 (Sept.) 1927. Scott, R. W., and Saphir, O. *The Pathogenesis of Syphilitic Aortic Insufficiency*, Tr. A. Am. Physicians **42** 36, 1927.

8 Buchbinder, W. C., and Saphir, O. *Heart Failure in Subacute Bacterial Endocarditis*, Arch. Int. Med. **64** 336 (Aug.) 1939.

9 Kastner, A. *Ueber Endocarditis lenta*, Deutsches Arch. f. klin. Med. **126** 370 (June) 1918.

of the criteria set forth in the preceding section the syphilitic nature of the valvular deformity cannot be regarded as proved

Briggs¹⁰ (1922) reviewed the literature and added a proved instance of acute verrucous endocarditis of the aortic and the mitral valve with typical syphilitic aortic insufficiency (separation of the aortic commissures) and syphilitic aortitis, which had followed a subacute course. Blood cultures disclosed nonhemolytic streptococci, and the Wassermann reaction of the blood was positive.

Curschmann¹¹ (1922) observed a clinical instance of "endocarditis lenta" and aortic insufficiency, in which the Wassermann reaction of the blood was positive. The blood culture revealed a streptococcus similar in characteristics to the pneumococcus. However, since the patient related a remote history of recurrent acute rheumatic fever, one cannot regard this case as proved without anatomic confirmation.

Blumer¹² (1923) found only 1 instance among records of 330 collected cases of subacute bacterial endocarditis in which "an old valve lesion" and a history of syphilis were mentioned. No further details concerning this case are given, but the appended bibliography indicates that it is likely that it is the one described by Kastner.⁹

In a study of 35 cases of streptococcic aortic endocarditis, Thayer¹³ (1926) observed 2 cases of syphilitic aortitis, but there was "little evidence to suggest syphilitic disease of the aortic valve in any case." In his group of cases of acute bacterial endocarditis due to *Staphylococcus albus*, in only 1 instance was the disease superimposed on a preexisting syphilitic aortic insufficiency with accompanying syphilitic aortitis.

Pineles¹⁴ (1926) recorded 4 cases in which there was clinical evidence of syphilitic aortitis and aortic insufficiency and in which signs of subacute bacterial endocarditis subsequently developed. In only 1 instance (case 4) was an autopsy performed, revealing verrucous endocarditis of the aortic valve and syphilitic aortitis with encroachment on the aortic leaflets, the blood culture was negative, and the Wassermann reaction of the blood weakly positive. Although there is strong evidence favoring the clinical diagnosis of syphilitic aortic insufficiency in the remaining 3 cases, its coexistence with bacterial endocarditis cannot be accepted as proved without necropsy.

10 Briggs, L. H. Bacterial Endocarditis as a Sequel to Syphilitic Valve Defect, *Am J M Sc* **164** 275 (Aug) 1922

11 Curschmann, H. Ueber Endocarditis chronica (lenta), *München med Wchnschr* **69** 419 (March 24) 1922

12 Blumer, G. Subacute Bacterial Endocarditis, *Medicine* **2**:105, 1923

13 Thayer, W. S. Studies on Bacterial (Infective) Endocarditis, *Johns Hopkins Hosp Rep* **22** 1 1926

14 Pineles, F. Aortenlues und Endocarditis lenta. *Med Klin* **22** 444 (March 19) 1926

Cade¹⁵ (1927) observed an instance of syphilitic aortitis associated with vegetative aortic and mitral endocarditis. The aortic cusps were indurated, retracted and insufficient, but without a description of the commissures the presence of syphilitic changes in the aortic valve remains in doubt.

Sumbal¹⁶ (1928) reported 18 instances in which the conditions were diagnosed clinically as syphilis associated with subacute bacterial endocarditis. In 10 of these, postmortem examinations were made. In 5 the underlying valvular deformity was either typically rheumatic or very probably rheumatic, according to the protocols, for the remaining 5 no anatomic description of the aortic valves is recorded beyond that of the vegetations, in only 1 was syphilitic aortitis observed, and in this instance the aortic valve is not described. Skursky¹⁷ (1929) cited 2 cases of malignant endocarditis of the aortic valve associated with syphilitic aortitis (necropsy). Again, the protocols offer no comment concerning the possibility of syphilitic involvement of the aortic valve or about the state of the aortic commissures.

Schnabel and Levy¹⁸ (1931) recorded a proved instance of acute bacterial endocarditis superimposed on a syphilitic deformity of the aortic valve. The Wassermann reaction of the blood was strongly positive, and clinical and anatomic evidence of *tabes dorsalis* was found. Blood cultures were negative. Lemann¹⁹ (1931) observed an instance of subacute bacterial (pneumococcal) endocarditis with aortic insufficiency in a patient with a history of syphilis. The Wassermann reaction of the blood was strongly positive, and clinical signs of neurosyphilis were elicited. Only the following brief anatomic description of the heart is given: "The valves on the left side presented large cauliflower-like growths." There are no remarks concerning the aorta. Although Lemann submitted that "we are probably justified in assuming that this aortic regurgitation had been produced by the syphilitic process," it is apparent that the anatomic evidence, according to the record, is distinctly lacking. A chronologic review of the clinical history shows that manifestations of bacterial endocarditis were already

15 Cade, M. A. Endocardite infectieuse à marche lente greffée sur une aortite syphilitique, *Lyon med* **139** 731 (June 19) 1927.

16 Sumbal, J. Case of Endocarditis Due to Untreated Syphilitic Infection, *Bratisl lekar listy* **8** 267 (May), 281 (June) 1928.

17 Skursky, J. Über Falle maligner Endokarditis bei Aortenlues, *Wein klin Wchnschr* **42** 293 (March 7) 1929.

18 Schnabel, T. G., and Levy, F. E. *Tabes Dorsalis, Syphilitic Aortitis, Aortic Regurgitation, and Bacterial Endocarditis*, *M. Clin North America* **15** 325 (Sept.) 1931.

19 Lemann, I. I. Subacute Bacterial Endocarditis (Pneumococcal) Engrafted upon Preexisting Syphilitic Valvular Disease, *Internat Clin* **2** 66 (June) 1931.

present when aortic regurgitation was first noted, and therefore they can offer no assistance in determining the onset of the latter

Fulton and Levine²⁰ (1932) analyzed 111 clinical cases of subacute bacterial endocarditis, and noted but 1 instance which might be regarded as illustrative of this combination. They concluded that "syphilis as a predisposing agent in streptococcus endocarditis is extremely rare." Craven²¹ (1932) reviewed the literature and added a proved instance of syphilitic aortitis and aortic insufficiency complicated by aortic endocarditis due to *Str. viridans*.

Brahic, Recordier and Sarradon²² (1934) reported in abstract the case of a 45 year old patient who had manifested signs of syphilitic aortic insufficiency and later showed evidence of subacute bacterial endocarditis. Blood cultures were repeatedly negative. At necropsy, vegetative aortic endocarditis was observed, but no further description of the heart and aorta is recorded. Although the title of the abstract offers confirmation, further data are necessary before this case can be accepted as proved.

Perry²³ (1936) commented on the rarity of this combination and presented photographic evidence of subacute bacterial endocarditis engrafted on a typical syphilitic valvular deformity, the separation of the commissures being clearly demonstrable. Smith²⁴ (1937) and McMillan and Wilbur²⁵ (1937) added single proved instances, and Martin and Adams²⁶ (1938) reported 2 proved cases (cases 1 and 4) of bacterial endocarditis engrafted on typical syphilitic aortic valves. Of Martin and Adams' remaining 3 cases, 2 were of syphilitic aortitis with recent vegetative aortitis, but the aortic leaflets were normal. The fifth case was an instance of acute vegetative endocarditis (*Str. viridans* and *Escherichia coli*) of the mitral cusp of the aortic valve, with aortic insufficiency and syphilitic aortitis, but no comment on the aortic commissures is included in the protocol.

20 Fulton, M. N., and Levine, S. A. Subacute Bacterial Endocarditis, with Special Reference to the Valvular Lesions and Previous History, *Am J M Sc* **183** 60 (Jan) 1932.

21 Craven, E. B., Jr. Syphilitic Aortic Endocarditis and Superimposed Bacterial (*Streptococcus Viridans*) Endocarditis, *Am J Path* **8** 81 (Jan) 1932.

22 Brahic, J., Recordier, M., and Sarradon, P. Endocardite lente greffée sur une sigmoïdite aortique spécifique, *Marseille méd* **1** 766 (June 15) 1934.

23 Perry, C. B. Bacterial Endocarditis, Bristol, England, John Wright & Sons, Ltd., 1936.

24 Smith, F. J. The Coexistence of Syphilis of the Aorta and Bacterial Endocarditis. A Report of Three Cases, *Internat Clin* **2** 1 (June) 1937.

25 McMillan, R. L., and Wilbur, E. L. Staphylococcal Endocarditis Superimposed on Syphilitic Aortic Endocarditis, *J A M A* **109** 1194 (Oct 9) 1937.

26 Martin, H. E., and Adams, W. L., Jr. Bacterial Endocarditis Superimposed on Syphilitic Aortitis and Valvulitis. A Clinicopathological Study with Five Case Reports, *Am Heart J* **16** 714 (Dec) 1938.

Gallavardin and Gravier ²⁷ (1927), Raybaud, Jouve and Farnier ²⁸ (1935) and Areta ²⁹ (1935) observed single instances of subacute bacterial endocarditis associated with syphilitic aortitis, but in none was there evidence of syphilitic valvular disease. Another case recorded by François and Jouve ³⁰ (1934) revealed neither conclusive evidence of syphilitic aortitis nor anatomic signs of syphilis of the aortic valve.

Musser ³¹ (1933), Keefer ³² (1937), White ³³ (1937) and Hamman and Brown ³⁴ (1937) are but an added few of the recent authors who have remarked on the rarity with which subacute bacterial endocarditis involves syphilitic aortic valvular lesions. Curiously, such authoritative textbooks on pathology as that of Boyd ³⁵ (1935) and that of Muir ³⁶ (1936) do not mention syphilis as a predisposing factor, nor does Stokes ³⁷ in his book "Modern Clinical Syphilology."

Thus, in summary (table 1), it may be said that since Libman's original observation of the infrequent association of subacute bacterial endocarditis with syphilitic aortic valvular disease, only 7 proved instances of such a condition have appeared in the literature. In 3 others, the complicating endocarditis was of the acute form, making a total of 10 proved cases of bacterial endocarditis engrafted on syphilitic valves. In 4 more, in view of the incomplete descriptions in the protocols, the

27 Gallavardin, L, and Gravier, L. Endocardite infectieuse greffée sur aortite spécifique, *Lyon med* **139** 727 (June 19) 1927.

28 Raybaud, A, Jouve, A, and Farnier, G. Maladie de Jaccoud-Osler greffée sur une aortite chronique syphilitique, *Bull et mem Soc med d hôp de Paris* **51** 136 (Feb 4) 1935. Raybaud, A, and Jouve, A. Endocardite maligne lente (maladie de Jaccoud-Osler) et lésions aortiques syphilitiques, *J de med et chir prat* **106** 282 (April) 1935.

29 Areta, T. Endocarditis lenta maligna con aneurisma de la radial, *Semana med* **2** 645 (Aug 29) 1935.

30 François, L, and Jouve, A. Endocarditis maligne greffée sur une aortite syphilitique, *Marseille med* **2** 726 (Dec 15) 1934.

31 Musser, J. H. Subacute Bacterial Endocarditis, *Ann Int Med* **7** 715 (Dec) 1933.

32 Keefer, C. S. Subacute Bacterial Endocarditis. Active Cases Without Bacteremia, *Ann Int Med* **11** 714 (Nov) 1937.

33 White, P. D. Heart Disease, ed 2, New York, The Macmillan Company, 1937, p 257.

34 Hamman, L, and Brown, T. M. Subacute Bacterial Endocarditis, *Internat Clin* **3** 33 (Sept) 1937.

35 Boyd, W. The Pathology of Internal Diseases, ed 2, Philadelphia, Lea & Febiger, 1935, p 33.

36 Muir, R. Text-Book of Pathology, ed 4, Baltimore, William Wood & Company, 1936.

37 Stokes, J. H. Modern Clinical Syphilology, ed 2, Philadelphia, W. B. Saunders Company, 1934, pp 539 and 1053.

coexistence of syphilitic valvular deformities must be regarded as doubtful, and in 29, the presence of syphilitic disease of the aortic valve remains unproved (tables 2 and 3)

TABLE 1—*Proved Cases of Bacterial Endocarditis Superimposed on Syphilitic Aortic Valvular Disease*

Author	Age	Sex	Acute Type	Subacute Type	Organism
Briggs	35	M		1	Nonhemolytic streptococcus
Thayer			1		Staph albus
Pineles	54	M		1	
Schnabel and Leivy	50	F	1		
Craven	23	M		1	Str viridans
Perry				1	Not stated
Smith	63	M	1		Staph albus
McMillan and Wilbur	47	M		1	Staph haemolyticus aureus
Martin and Adams	60	M		1	Str viridans
	28	M		1	Str viridans
			3	7	

TABLE 2—*Doubtful Cases of Bacterial Endocarditis Superimposed on Syphilitic Aortic Valvular Disease*

Author	Age	Sex	Acute Type	Subacute Type	Organism
Kastner	32	F		1	Str viridans
Oade	42	M		1	Not stated
Brahic, Recordier and Sarradon	45	M		1	
Martin and Adams	42	M	1		Str viridans and E coli
			1	3	

TABLE 3—*Unproved Cases of Bacterial Endocarditis and Syphilitic Aortic Valvular Disease*

Author	Acute Type	Subacute Type	Organism	Comment
Cursehmann		1	Streptococcus	No autopsy
Pineles		1	Str viridans	No autopsy
		2		No autopsies
Gallavardin and Gravier		1	Not stated	Syphilitic aortitis alone
Sumbal		18	Not stated	Autopsies in 10, syphilitic aortitis in only 1 of the 10 (uncomplicated)
Skursky		1		No reference to syphilitic disease of aortic valve
		1	Not stated	
Lemann		1	• Pneumococcus	Anatomic description inconclusive
François and Jouve		1		Inconclusive anatomic evidence of syphilis
Ribaud, Jouve and Larnarier		1	Streptococcus	Syphilitic aortitis without extension to valve
Arel		1		Syphilitic aortitis without extension to valve
		29		

MATERIAL

In close accordance with the aforementioned diagnostic criteria, the case reports to be presented were culled from the clinical and necropsy material available at the Michael Reese and the Cook County Hospital and from my own clinical

case records Only those cases were selected in which the pathologic diagnosis of syphilitic disease of the aortic valve was unequivocal

Of 45 cases of bacterial endocarditis (1, acute, 44, subacute) among a total of 3,143 cases in which necropsy was performed at the Michael Reese Hospital during the ten year period from 1929 to 1938, in 2 (1, acute, 1, subacute) the disease was engrafted on a preexisting syphilitic aortic insufficiency, in 1 it had developed on a congenital bicuspid aortic valve damaged by syphilis, and in 1 there was syphilitic aortitis alone At the Cook County Hospital during the same ten year period, 228 cases of bacterial endocarditis (31, acute, 197, subacute) were observed among a total of 11,666 cases in which necropsy was done Of these, in 5 (1, acute, 4, subacute) the disease had developed on syphilitic aortic valves In 10 others it was associated with syphilitic aortitis, but the aortic valves were either normal or affected by disease other than syphilis

REPORT OF CASES

CASE 1—J R, a white man aged 60, was seen on April 13, 1936, because of cough, expectoration, dyspnea and weakness He had been in excellent health until one and a half years before, when progressive weakness and dyspnea became apparent He had been coughing frequently for four months, expectorating large amounts of colorless mucus On March 6 a transient, sudden and severe backache in the left part of the lumbar region developed Recently, sudden pain appeared in the left foot, radiated to the thigh and lasted three days He had lost 4 pounds (1.8 Kg) in four months

Past History—In December 1935 a tooth was extracted because of a periapical abscess No history of rheumatic fever, chorea or syphilis could be elicited With the exception of the dental infection, the history was noncontributory

Physical Examination—Examination on admission revealed a well developed, well nourished man, who appeared dyspneic and slightly pale The temperature was 100 F (oral), the respiratory rate was 28, and the pulse rate, 92 per minute The pupils were slightly irregular, but reacted well to light and in accommodation Examination of the heart disclosed an apical impulse, visible, heaving and localized in the fifth interspace in the midclavicular line The right border was 6 cm from the midsternal line in the fourth interspace, and the left border was 11 cm to the left in the fifth interspace A loud blowing systolic murmur was audible over the entire precordium, most intense at the apex and in the aortic area A prolonged blowing diastolic murmur was heard at the third left interspace near the sternal border and was transmitted to the right first interspace, over the sternum, to the apex The aortic second sound was accentuated and louder than the pulmonic second sound There was a Corrigan pulse, as well as a capillary pulse and a positive Duroziez's sign The radial arteries were thickened, and the brachial arteries were tortuous and pulsating Examination of the lungs revealed impaired resonance at the bases posteriorly, with many subcrepitant rales, there was hyperresonance elsewhere The liver edge was palpated 8 cm below the costal margin on inspiration, and was sharp, smooth and tender The spleen was palpable on inspiration, and the edge was rounded There was slight pretibial edema The patellar reflexes were hyperactive, and no achilles tendon reflexes were elicited The fingers were hippocratic The rest of the examination gave negative results The blood pressure was 145 systolic and 50 diastolic

Laboratory Examination—The urine had a specific gravity of 1.018 with an albumin content of 1 plus and no sugar, microscopic examination of the urine

showed 2 to 10 erythrocytes per high power field. Analysis of the blood revealed a hemoglobin value of 70 per cent (Sahli), erythrocytes, 4,000,000 per cubic millimeter, and leukocytes, 11,200, with a normal differential count. The Wassermann reaction of the blood was 1 plus, and the Kahn reaction, 4 plus. A culture of the blood revealed *Str. viridans*. A teleroentgenogram showed the cardiothoracic ratio to be 180/290 cm, the contour of the left side of the heart normal and the right border far beyond normal limits. The blood culture and the Wassermann and Kahn tests were repeated on April 20, with identical results. At this time it was learned that the patient had received antisyphilitic treatment in the past.

Course—Recurrent showers of petechiae appeared on the abdomen, extremities, eyelids, thorax and back. Pain in the left upper quadrant associated with splenic swelling and tenderness and a rise in temperature occurred at infrequent intervals and subsided in four to five days. On May 1 there was transitory diplopia. The apical systolic murmur became louder and rough, and a diagnosis of vegetative endocarditis of the mitral valve was made. The general course of the illness was progressively downhill. One week before death, examination of the blood disclosed hemoglobin, 50 per cent, erythrocytes, 2,700,000 per cubic millimeter, and leukocytes, 12,000. The fever was intermittent, with afebrile periods of one to two days, the average temperature was from 99 to 100 F (oral), and occasionally it was 103.4 F. Death occurred on November 6, following bilateral bronchopneumonia. The diagnosis was as follows: subacute bacterial endocarditis (aortic and mitral), syphilitic aortic insufficiency, syphilitic aortitis and neurosyphilis.

Autopsy (performed by Dr. M. Lev)—*Gross Examination*. The heart weighed 550 Gm. The mitral leaflets presented numerous semifrable vegetations. The aortic cusps were moderately thickened, and their edges were rolled. There was a moderate separation of all three commissures. The right anterior cusp was covered by a mass of small vegetations extending over the upper portion of the muscular ventricular septum and over the anterior portion of the pars membranacea. Small groups of vegetations were observed on the left anterior, and a few on the posterior, aortic cusp. The mouth of the right coronary artery was restricted by grayish blue puckered plaques. The aorta was covered by a conglomeration of plaques, and the intima was wrinkled and puckered (figs. 1 and 2).

Microscopic Examination. The cusp of the aortic valve was denuded from the epithelium and was covered by clumps of fibrin which showed small cocci arranged in chains. The edges of the cusp revealed smaller and larger areas of necrosis. The cusp itself showed a number of spindle-shaped cells arranged in the form of bands, as well as lymphocytes and endothelial leukocytes. Close to the base of the cusp, there were areas of hyalinization and several blood vessels surrounded by lymphocytes. Examination of the aorta revealed in the adventitia a new formation of connective tissue, with hyalinization of many of the connective tissue fibers. Some of the vasa vasorum showed marked intimal proliferation. There was an extensive infiltration of lymphocytes in the perivascular spaces. The media revealed interruptions in the course of the elastic fibers as well as connective tissue replacement and a number of small blood vessels, surrounded by lymphocytes. The intima contained areas of fibrosis, hyalinization and calcification.

The pathologic diagnosis was as follows: syphilitic aortitis, syphilitic aortic insufficiency, restriction of the mouth of the right coronary artery and subacute bacterial endocarditis of the aortic and the mitral valve.

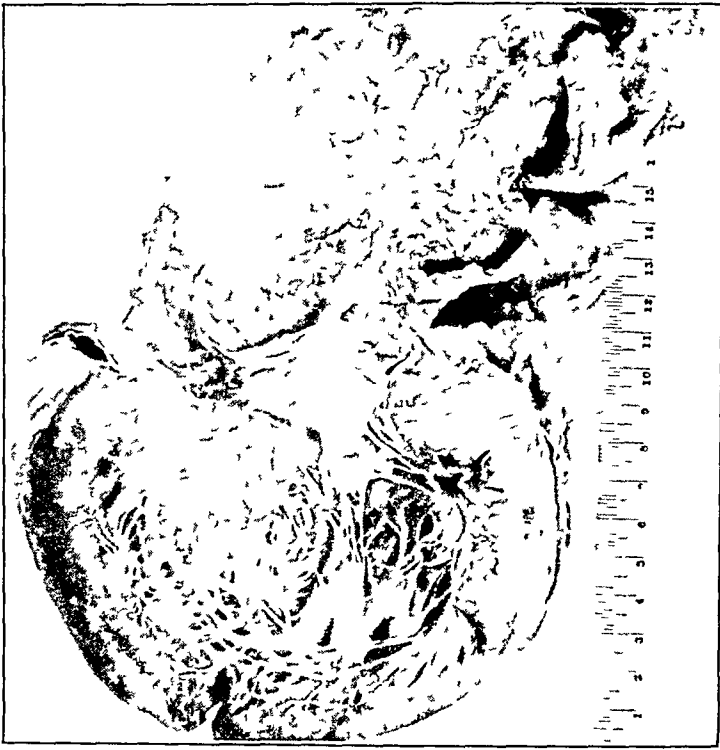


Fig 1—Heart and aorta, showing syphilitic aortitis and aortic insufficiency as well as subacute bacterial endocarditis of the aortic and the mitral valve



Fig 2—Heart and base of the aorta under higher magnification, showing wrinkling and puckering of the aortic intima, restriction of the mouth of the right coronary artery, separation of the aortic commissures, vegetations (especially on the aortic cusps) and ulceration of an aortic and a mitral leaflet

CASE 2—J J, a white man aged 56, was admitted to the Michael Reese Hospital on Oct 7, 1938, complaining of choking spells and constipation. In 1931 progressive weakness, swelling of the legs and dyspnea on exertion set in. A "leaking aortic valve" was observed at this time. Rest and reduction in weight effected considerable improvement. In the last three years the dyspnea had grown worse, and increasing weakness and swelling of the ankles and feet recurred. Three weeks before admission generalized aching and cough appeared. The dorsum of the left foot became reddened, tense and shiny but improved within five days. The dyspnea, weakness and orthopnea were decidedly worse thereafter, and paroxysmal nocturnal dyspnea developed. The patient had been markedly constipated for three weeks, had had no appetite and had vomited on two occasions. He had lost 20 pounds (9 Kg) in two years.

Past History—The patient had gonorrhea and a chancroid at the age of 20 years. In 1930 his wrists became painful and swollen (?), and there was generalized muscular pain lasting three days. The past history otherwise was without significance.

Physical Examination—On admission the patient appeared fairly well nourished, well developed, slightly dyspneic and orthopneic. The temperature was 99.8 (rectal), the pulse rate was 98, and the respiratory rate 22, per minute. The skin and mucous membranes were pale. The tonsils were enlarged. There were marked arterial and venous pulsations in the neck. The lungs were normal except for occasional subcrepitant rales at the bases posteriorly. The apical impulse was palpable and visible in the fifth interspace just outside the midclavicular line. The cardiac dulness was slightly increased to the right and moderately to the left. Blowing systolic and diastolic murmurs were audible at the apex and right base, and a blowing systolic murmur was heard over the pulmonic area. There was a Corrigan pulse. The liver was palpated 10 cm below the costal margin and was sharp and tender. The spleen was 4 cm below the costal margin. Clubbing of the fingers and edema of the sacrum, legs and feet were observed. The blood pressure was 146 systolic and 42 diastolic.

Laboratory Examination—The value for hemoglobin was 75 per cent, for erythrocytes 3,550,000 per cubic millimeter and for leukocytes 14,300, with a differential count of 77 per cent polymorphonuclears, 15 per cent lymphocytes, 2 per cent myelocytes, 5 per cent immature leukocytes and 1 per cent metamyelocytes. Polychromatophilia was present. Wassermann and Kahn tests gave readings of 4 plus. The urine had a specific gravity of 1.016 and an acid reaction. There was a 2 plus reaction for albumin. Occasional leukocytes and erythrocytes and a few hyaline casts were observed. The nonprotein nitrogen value was 76 mg per hundred cubic centimeters. A teleoroentgenogram showed an increased cardiothoracic ratio of 19.5/32.6 cm, a prominent ventricular bow, a straightened left border and a wide aortic diameter. A blood culture was negative.

Course—The temperature varied from 99.6 to 102 F (rectal). The pulse rate was 80 to 100 per minute. Dyspnea and restlessness were prominent. Death occurred suddenly on October 12. The diagnosis was as follows: subacute bacterial endocarditis (?), syphilitic aortitis and aortic insufficiency, myocardial hypertrophy and dilatation and advanced congestive heart failure.

Autopsy (performed by Dr. M. Lev)—*Gross Examination*. The heart weighed 575 Gm. The aortic cusps were moderately thickened and retracted, with distinct separation of the commissures. On the left anterior cusp there was a grayish yellow, adherent vegetation about 1.2 cm in length. A smaller similar vegetation was

observed on the posterior cusp. The aortic leaflet of the mitral valve presented many large, confluent, grayish yellow, adherent vegetations. The ostium of the left coronary artery was distinctly narrowed. The ascending limb of the aorta was moderately dilated. The lining exhibited multiple bluish gray, longitudinally wrinkled plaques, most marked at, and just above, the aortic valve.

Microscopic Examination—The vegetations presented a mass of polymorphonuclear leukocytes lying in a homogeneous material which stained pink. The aorta showed many mononuclear cells infiltrating the media and surrounding the vasa vasorum in the adventitia. The intima was thickened and hyalinized.

The pathologic diagnosis was syphilitic aortitis with aneurysmal dilatation of the ascending part of the aorta and narrowing of the left coronary ostium, syphilitic aortic insufficiency and acute vegetative endocarditis of the aortic and the mitral valve.

CASE 3—J. H., a Negro aged 45, was admitted to the Cook County Hospital on Feb. 14, 1930, complaining of frontal headache, throbbing pains in the head and dizziness of two and a half months' duration. He had also noted palpitation and slight dyspnea on exertion for several months. Three days before admission "everything went black" before his eyes, and the left upper extremity became paralyzed, although consciousness was retained.

Past History—Except for a penile sore thirty years ago the previous history was noncontributory.

Physical Examination—The patient was well developed and well nourished. He was unable to move the left upper extremity. The temperature was 99.8 F (oral), the pulse rate was 100, and the respiratory rate 24, per minute. The pupils reacted sluggishly to light but well in accommodation. The left nasolabial fold was smooth, there was drooping of the left angle of the mouth. The teeth were carious. There were marked arterial pulsations in the neck. Examination of the heart showed the apical impulse to be visible, forceful and palpable in the sixth interspace. The left border was 12 cm from the midsternal line in the sixth interspace, and the right border was 4 cm to the right in the fourth interspace. There were blowing systolic and diastolic murmurs over the entire precordium, loudest over the aortic area. Corrigan pulse and capillary pulse were observed, and Duroziez's sign was present. The left upper extremity was flaccid. Patellar and achilles tendon reflexes were absent, the Babinski reflex was normal, and the left cremasteric reflex was absent. The rest of the examination gave negative results. The blood pressure was 150 systolic and 90 diastolic.

Laboratory Examination—The urine was normal. The Wassermann reaction of the blood was negative. Tests of the spinal fluid revealed no abnormalities. Clinical analysis of the blood showed a hemoglobin value of 45 per cent, an erythrocyte count of 2,500,000 per cubic millimeter and a leukocyte count of 16,500. A teleoroentgenogram showed marked prominence of the aortic arch. Blood cultures taken on April 30, May 12 and May 26 yielded a moderately long chain streptococcus with a definite capsule. It could not be identified by subculture, but was neither *Str. viridans* nor *Str. haemolyticus*.

Course—Weakness, pain in the left hypochondrium and swelling of the feet developed. Nocturia occurred. Petechiae appeared. The spleen became palpable. The temperature averaged 100 to 101 F (oral), with a maximum of 103 F. The pulse rate ranged from 90 to 110 per minute. The course was progressively downhill, terminating in stupor and death on July 20. The diagnosis was subacute bacterial endocarditis, syphilitic aortitis and aortic insufficiency.

Autopsy (performed by Dr R H Jaffe) —Gross Examination The heart weighed 600 Gm On the anterior cusp of the mitral valve there were two soft, adherent, polypoid, yellow-gray deposits measuring 5 by 3 mm In the middle of the cusps there was an irregular hole 3 by 2 mm in diameter, and at the lower edge were soft, pink-gray, polypoid deposits 7 by 5 by 15 mm Above the hole a thin-walled, yellowish pink outpouching was observed The aortic cusps were slightly thickened and showed separation of the commissures as well as synechiae between the commissures and the wall of the aorta The right cusp showed a large, soft, yellow-gray deposit 22 by 08 by 07 cm Granular and nodular deposits of similar material extended over the ventricular aspect of the posterior leaflet Examination of the aorta revealed extensive wrinkling of the intima throughout the ascending portion and the arch

Microscopic Examination The aorta showed numerous flame-shaped scars throughout the media, with adjacent areas of diffuse necrosis Cellular granulation tissue penetrated the media

The pathologic diagnosis was thromboendocarditis of the aortic and the mitral valve, syphilitic aortic insufficiency and aortitis

CASE 4—W M, a white man, aged 36, was admitted to the Cook County Hospital on Feb 7, 1933, complaining of shortness of breath and pain in the chest and neck Five weeks before, dyspnea was noted on exertion Shortly thereafter, pallor of the skin, aching pain behind the sternum and along the sides of the neck, dull epigastric pain, palpitation and decreasing appetite appeared These symptoms temporarily improved when the patient rested in bed, but became progressively worse when he resumed work A dry cough and orthopnea developed, and, together with the other symptoms, persisted to the time of admission

Past History—The previous history was irrelevant except for probable rheumatic fever at the age of 6 years, but the details of this illness were obscure No history of syphilis could be elicited

Physical Examination—The man was pale and dyspneic and appeared critically ill The lips and nail beds were slightly cyanotic The temperature was 96.6 F (oral), the pulse rate was 96, and the respiratory rate 24 per minute The conjunctivas and the buccal mucosa were pale The mouth was edentulous The submaxillary nodes were slightly enlarged There were vigorous arterial pulsations in the neck Dulness with subcrepitant rales was observed at the bases of the lungs posteriorly The heart was enlarged, with a diffuse apical impulse in the left anterior axillary line in the sixth interspace The right border was 5 cm from the midsternal line in the fourth interspace Blowing systolic and diastolic murmurs were heard over the entire precordium, the latter being loudest at the left third interspace Corrigan pulse, capillary pulse and Duroziez's sign were elicited The abdomen was moderately distended with fluid The liver was palpated 12 cm below the costal margin and was tender The spleen was felt 4 cm below the costal margin Pretibial and sacral edema were observed The blood pressure was 150 systolic and 80 diastolic

Laboratory Examination—The urine contained albumin (3 plus) and no sugar Microscopic study of the urine revealed occasional erythrocytes, leukocytes and epithelial cells Analysis of the blood showed a hemoglobin value of 78 per cent (Sahli), an erythrocyte count of 4,470,000 per cubic millimeter and a leukocyte count of 29,000, with a differential count of 80 per cent polymorphonuclears, 2 per cent myelocytes, 4 per cent metamyelocytes, 7 per cent small lymphocytes and 7 per cent monocytes Culture of the blood showed no growth

Course—Death occurred the following day. The maximum temperature was 100.6 F (rectal).

Autopsy (performed by Dr. V. Levine)—*Gross Examination*. The heart weighed 660 Gm. The aortic valve showed a moderate separation of the commissures between the posterior and the right leaflet and the posterior and the left leaflet. There were fenestrations at the attachment of the left and posterior leaflet. The commissure between the right and the left aortic cusp was missing, and there was a gap 4 cm. in diameter between them. A purple-gray vegetation 0.5 by 1.0 by 0.1 mm. was attached to the left cusp. The right leaflet was thickened (3 mm.) and covered with gray nodules of pinhead size. The aorta showed marked scarring and wrinkling extending to the commissures.

Microscopic Examination. The aortic cusps showed cellular and vascular tissue rich in fibrocytes, small round cells and histiocytes and having an occasional neutrophilic leukocyte. The subendothelial layer was thickened and the uppermost layer presented, in places, fibrinoid necrosis. Examination of the aorta showed the adventitia to be thickened and hyalinized and to have a marked perivascular infiltration of lymphocytes with an occasional plasma cell and histiocyte. The media was thickened, newly formed capillaries extended to the intima and presented a decided perivascular infiltration of plasma cells, histiocytes and a few lymphocytes. Cultures of the spleen showed no abnormalities. The Kahn test of the blood taken post mortem gave a negative reading. The Wassermann test was anti-complementary. The pathologic diagnosis was syphilitic aortic insufficiency, syphilitic aortitis and verrucous endocarditis of the aortic valve.

CASE 5—M. J., a Negress aged 45, was admitted to the Cook County Hospital on Jan. 20, 1934, complaining of fever and loss of weight. For three months she had been restless, tremulous and easily upset. She had felt feverish in the evenings and had been losing weight steadily. Nocturia was present, and she had been having pain in the left posterior portion of the lumbar region, radiating to the left hypochondrium.

Past History—Except that the first pregnancy terminated in a miscarriage, the past history was irrelevant. The patient stated that she had never had a venereal disease.

Physical Examination—The patient appeared fairly well nourished, well developed and not acutely ill. The temperature was 98.8° F (oral), the pulse rate was 100, and the respiratory rate 20, per minute. The pupils were miotic and equal, they reacted sluggishly to light but well in accommodation. The conjunctivas and the buccal mucosa were pale. Examination of the lungs revealed impaired resonance and diminished tactile fremitus as well as suppressed breath sounds and subcrepitant rales at the right base posteriorly. The heart was slightly enlarged, with the left border at the nipple line. A soft blowing systolic murmur was heard at the right base, and a blowing diastolic murmur at the third left interspace near the sternum was transmitted to the right and downward. The aortic second sound was accentuated. Pain on pressure was elicited in the left hypochondrium. The fingers were slightly hypocratic. The patellar and achilles tendon reflexes were sluggish. The rest of the examination gave negative results. The blood pressure was 90 systolic and 40 diastolic.

Laboratory Examination—The urine contained albumin (1 plus) and no sugar, microscopically, hyaline and many granular casts were observed. The hemoglobin value of the blood was 55 per cent, and the leukocytes numbered 8,700 per cubic millimeter, with a differential count of 56 per cent polymorphonuclears, 38

per cent small lymphocytes, 2 per cent basophils and 4 per cent monocytes The Kahn reaction was 4 plus Culture of the blood yielded *Str viridans* A teleoroentgenogram showed moderate cardiac enlargement with passive congestion at the bases of the lungs

Course—The clinical course was progressively downhill A low grade remittent fever, averaging 100 to 102 F (oral), was present daily Death occurred on March 12 The diagnosis was syphilitic aortitis, syphilitic aortic insufficiency with engrafted subacute bacterial endocarditis and neurosyphilis

Autopsy (performed by Dr R H Jaffé)—The heart weighed 300 Gm The commissures of the aortic leaflets were separated for a distance of about 6 mm The right and the left leaflets near the commissures were thickened and nodular On the right leaflet there was a soft, adherent, purple-gray mass, 10 by 11 by 6 mm The aortic surface of the other leaflets was covered by purple-gray, granular deposits measuring up to 4 by 2 by 1 mm The aorta showed an irregular wrinkling and puckering of the intima, extending to the upper third of the descending thoracic aorta

The pathologic diagnosis was malignant endocarditis of the aortic valve, syphilitic aortic insufficiency and syphilitic aortitis

CASE 6—M L, a Negress aged 42, was admitted to the Cook County Hospital on March 8, 1934, complaining of pains over the body, weakness and fever Four months before admission she had noted soreness in the bones and swelling and pain over the dorsum of the left hand with limitation of motion Shortly thereafter, pain appeared in the knees and ankles She had had fever for several weeks and had become progressively weaker Knifelike pains above the right hip and shooting pains in the head had been present for seven to ten days

Past History—In 1925 the patient was bedridden for a short period, suffering from painful knees and ankles and swollen eyelids At that time her physician informed her of a "leak" in her heart and of the presence of anemia, but she improved and had been well since then

Physical Examination—The patient was fairly well nourished and slightly dyspneic The temperature was 100.6 F (oral), the pulse rate was 120, and the respiratory rate 28, per minute The pupils were contracted and slightly irregular and did not react to light, the scleras were hyperemic The tonsils were enlarged The cervical vessels pulsated visibly The lungs were normal except for subcrepitant rales at the bases posteriorly Examination of the heart revealed a diffuse precordial pulsation, the apex was just beyond the midclavicular line The cardiac dullness was slightly increased to the left Blowing systolic and diastolic murmurs were heard over the entire precordium, loudest at the base Corrigan pulse, capillary pulse and Duroziez's sign were observed The liver was palpated 4 cm below the costal margin in the nipple line on inspiration and was sharp and tender The spleen was felt 2 cm below the costal margin on inspiration, the edge was rounded and of increased consistency Patellar reflexes were absent The rest of the examination gave normal results The blood pressure was 178 systolic and 48 diastolic

Laboratory Examination—The hemoglobin of the blood was 55 per cent, the erythrocyte count was 3,000,000 per cubic millimeter and the leukocyte count 28,100 with 85 per cent polymorphonuclears and 15 per cent small lymphocytes Wassermann and Kahn tests of the blood gave reactions of 2 plus Urinalysis revealed no abnormalities except for occasional hyaline casts The Wassermann reaction of the spinal fluid was 4 plus Three blood cultures yielded no organisms

Course—Petechiae appeared in the conjunctivas. Fever (99 to 102 F) continued. On March 28 left hemiplegia developed suddenly (embolism). Coma ensued, terminating in death the following day. The diagnosis was syphilitic aortic insufficiency, bacterial endocarditis, syphilitic aortitis and neurosyphilis.

Autopsy (performed by Dr P. Melnick)—The heart weighed 465 Gm. The aortic leaflets were shrunken and thickened and presented numerous gray-red, granular vegetations. Similar vegetations were observed on the anterior wall of the left ventricle. The commissures separating the aortic leaflets were widened. The aorta showed marked wrinkling and puckering of the intima. Culture of the spleen yielded *Str. viridans*.

The pathologic diagnosis was malignant vegetative endocarditis of the aortic valve and mural endocarditis of the adjacent endocardium, syphilitic aortitis and syphilitic aortic insufficiency.

CASE 7—J. O., a white man, aged 54, was admitted to the Cook County Hospital on March 30, 1931. Eleven days before entrance he had a chill followed by fever, pain in the right side of the chest, shortness of breath and cough with expectoration of a thick, tenacious bloody sputum. The pain in the chest was intensified by deep inspiration and by coughing.

Past History—The patient had gonorrhea at 24 years of age but said he had not had syphilis. The rest of the history was irrelevant.

Physical Examination—The man was well developed and well nourished, slightly dyspneic, cyanotic and acutely ill. The temperature was 102 F (rectal), the pulse rate was 108, and the respiratory rate 28, per minute. The pupils were unequal and slightly irregular, but reacted to light and in accommodation. The pharynx was hyperemic. Examination of the lungs revealed dulness, increased tactile fremitus, bronchial breathing, whispered pectoriloquy, and subcrepitant rales over the upper lobe of the right lung. The heart was normal. The liver was palpated 2 cm. below the costal margin on inspiration. The patellar reflexes were sluggish, and the achilles tendon reflexes absent. The rest of the examination gave negative results.

Laboratory Examination—Urinalysis revealed no abnormalities. The Kahn reaction of the blood was 1 plus. The leukocytes numbered 10,600 per cubic millimeter.

Course—The temperature dropped to normal on April 6 but rose again on the following day. The pulse and respiration became accelerated, and gross hematuria appeared. Urinalysis showed the urine to be acid and to have a specific gravity of 1.012. There was a 2 plus reaction for albumin, and no sugar was present. Myriads of erythrocytes and occasional leukocytes were observed microscopically. On April 19 a to and fro murmur was audible at the apex and the base. The findings with reference to the lungs were unchanged. The temperature ranged from 98 to 103.6 F (rectal), the respirations were 24 to 28 per minute. Death occurred on April 20. The diagnosis was unresolved pneumonia, bacterial endocarditis and neurosyphilis (?).

Autopsy (performed by Dr S. Rosenthal)—*Gross Examination*. The heart weighed 415 Gm. The right aortic cusp was perforated by a polypoid, yellow-gray soft mass 1.5 by 0.2 cm. The first portion of the aorta presented numerous elevated, firm, grayish plaques showing wrinkling and puckering, especially in the commissures.

Microscopic Examination. The aorta showed subendothelial intimal thickening with round cell infiltration. There were numerous perivascular and focal round cell infiltrations in the adventitia and the media as well as scarring and rupture of the elastic lamina.

The pathologic diagnosis was postpneumonic thromboulcerative endocarditis of the aortic valve, syphilitic aortitis, syphilitic aortic insufficiency and lobar pneumonia of the upper lobe of the right lung, complicated by carnification and abscess

Other Cases—In 3 other instances of this series, bacterial endocarditis had developed on previously damaged aortic valves and was associated with syphilitic aortitis, but in the absence of a positive statement regarding the condition of the commissures they could not be accepted as proved instances of syphilitic aortic insufficiency. Similarly, I have not included in the reports the instance of subacute bacterial endocarditis engrafted on a congenital bicuspid aortic valve showing also the typical signs of syphilitic valvular involvement and associated with syphilitic aortitis, since bicuspid aortic valves are more often complicated by endocarditis than are syphilitic valves

COMMENT

Incidence—While the literature is replete with comments relative to the rarity with which bacterial endocarditis develops on syphilitic aortic valves, with few exceptions, little indication of the approximate incidence may be gleaned from the reports available at present. Thus, in a series of 198 cases of bacterial endocarditis, Thayer¹³ noted only 1 instance of acute endocarditis superimposed on syphilitic valves. Smith²⁴ observed a single instance (acute) in a series of 193 cases (acute and subacute), and recently Martin and Adams²⁶ reported 2 instances among 157 cases of subacute bacterial endocarditis collected from a total of 17,000 cases in which necropsy was performed. A further attempt to answer this question was made in the present study.

Of a total of 241 proved cases of subacute bacterial endocarditis collected from the records of the Cook County and the Michael Reese Hospital, in 5 the disease was observed to be engrafted on a preexisting uncomplicated syphilitic valvular deformity (2.1 per cent). These cases were selected from a series of 14,809 cases in which necropsy was done, the incidence being, therefore, 0.03 per cent. Although but few contributors to the literature have designated the number of cases of bacterial endocarditis observed at necropsy from which their studies were drawn, the available data (table 4) indicate that these combined lesions occurred in 7 of 590 instances of subacute bacterial endocarditis. Addition of the total necropsy figures of Martin and Adams²⁶ to those of the present report shows only 7 such instances among 31,809 cases in which autopsy was performed (0.02 per cent) (table 4).

A complete study of the cases of acute bacterial endocarditis observed at the Michael Reese Hospital could not be made, but a review of the necropsy records of syphilitic aortitis revealed only 1 instance

of unquestionable syphilitic aortic insufficiency complicated by acute bacterial endocarditis. Another case was found in the records of the Cook County Hospital among 31 instances of acute bacterial endocarditis. While this form of endocarditis is much less common than the subacute type, the limited material available indicates that it involves syphilitic valves with the same frequency as does the subacute variety (table 4).

The explanation of the infrequent involvement of syphilitic valves by bacterial endocarditis has evoked much thought and speculation. Briggs¹⁰ expressed the opinion that age incidence plays a significant role, since both rheumatic heart disease and bacterial endocarditis are more common among persons under the age of 35 years, whereas

TABLE 4—*Incidence of Bacterial Endocarditis and Syphilis of the Aortic Valve*

Author	Total Number of Ne cropsies	Acute Bacterial Endocarditis			Subacute Bacterial Endocarditis			
		Total Number of Cases	Cases Engrafted on Syphilitic Valves		Total Number of Cases	Cases Engrafted on Syphilitic Valves		
			No	%		No	%	% of Total Number of Necropsies
Thayer		177	1		21	0		
Smith		22	1		171	0		
Martin and Adams	17,000				157	2		
Rosenberg	14,809	32	2		241	5		
	31,809	231	4	1.7	590	7	1.3	0.02

syphilitic cardiovascular disease usually becomes manifest in older persons. Attractive as this idea may appear, the interpretation seems to be more subtle.

Perry²³ suggested that the comparative rarity of syphilitic heart disease, as observed in the principal teaching hospitals in Great Britain, might in itself be explanatory. But this view seems inadequate, for in the United States, among persons over 40 years of age syphilis is a common cause of aortic insufficiency. Perry postulated further that perhaps the shorter duration of life of patients with syphilitic heart disease, as compared with that of patients with rheumatic heart disease, presents fewer opportunities for the development of bacterial endocarditis. While this may be a factor, one must be reminded that even though the life expectancy is short once the symptoms of cardiovascular syphilis appear, the development of this advanced stage is long and insidious.

Another point of view has evolved from the belief, held by some investigators, that rheumatic fever and subacute bacterial endocarditis are but manifestations of the same infection and that this accounts for

their frequent association Von Glahn and Pappenheimer³⁸ reviewed the literature pertaining to this aspect of the subject and from their studies concluded that subacute bacterial endocarditis arises as a secondary bacterial infection implanted on unhealed rheumatic verrucae. Other investigators are in accord with the belief that these two diseases are of different origins. Indeed, the very occurrence of subacute bacterial endocarditis on syphilitic valves, even though rare, is another point in favor of the latter view, yet, on the other hand, it may bespeak the factor of coincidence.

Basing his conclusion on Koester's³⁹ view that infections of the valves of the heart arise from bacterial emboli lodging in the coronary capillaries, Briggs¹⁰ stated that the greater vascularization of rheumatic valves offered a cogent explanation for the higher incidence of subacute bacterial endocarditis in rheumatic hearts. In support of Koester's belief, Bayne-Jones⁴⁰ observed an increased vascularity in the valves damaged by the rheumatic virus. In his injection experiments, however, he noted that the increased network of capillaries reached the edges of the auriculoventricular valves, but ended along the basal part of the semilunar valves. These studies afford a feasible explanation for the susceptibility of rheumatic mitral valves to bacterial endocarditis but not for that of rheumatic aortic valves. The fact that one can also demonstrate an increased vascularity in syphilitic aortic valves detracts further from Briggs's hypothesis. Moreover, one cannot reconcile this view with the observation that bicuspid aortic valves, more often affected by subacute bacterial endocarditis than are syphilitic valves, show no increased vascularization (Perry²³) nor with Keefer's³² failure to demonstrate blood vessels in the valves of the heart of all subjects.

Saphir and Wile⁴¹ offered the explanation that the deformity of the aortic valves produced by syphilis results in decreased excursions of the cusps, thereby providing smaller areas for the settling of bacteria. In contrast, they stated that in cases of rheumatic and congenital diseases the aortic valves present larger areas than normal for bacterial implantation. This interesting observation has heretofore received

38 Von Glahn, W. C., and Pappenheimer, A. M. Relationship Between Rheumatic and Subacute Bacterial Endocarditis, *Arch Int Med* **55**:173 (Feb) 1935

39 Koester, K. Die embolische Endocarditis, *Virchows Arch f path Anat* **72** 257, 1878

40 Bayne-Jones, S. The Blood Vessels of the Heart Valve, *Am J Anat* **21** 449 (May) 1917

41 Saphir, O., and Wile, S. A. Rheumatic Manifestations in Subacute Bacterial Endocarditis in Children, *Am Heart J* **9** 29 (Oct) 1933

no consideration. Nevertheless, it would seem to be a contributory factor.

A review of the present state of knowledge indicates that bacterial endocarditis arises usually as a surface infection, invading the valves from without. Leary⁴² and Mallory and Keefer⁴³ were able to demonstrate this experimentally. Further, Grant, Wood and Jones⁴⁴ often observed platelet thrombi adherent to damaged heart valves and expressed the opinion that such thrombi, relatively free from leukocytes, form an ideal nidus for the localization and growth of bacteria. The importance of leukocytes as an effective and rapid bactericidal agent has recently been clearly demonstrated by Friedman, Katz and Howell⁴⁵ in their experimental study of endocarditis due to *Str. viridans*. It is of special interest then, that Grant, Wood and Jones⁴⁴ observed platelet thrombi more commonly in rheumatic valvular disease and on congenitally diseased bicuspid aortic valves and only infrequently in syphilitic valvular disease. They attributed this difference in part to the degenerative changes so often occurring in their cases in which there were rheumatic and congenitally defective bicuspid valves and not to thickening of the valves alone, for the latter likewise occurs in syphilitic valves.

Keefer³² pointed out that in the development of bacterial endocarditis four factors are important, namely (1) a previously damaged valve, (2) platelet thrombi on the valves, (3) transient bacteremia and (4) antibacterial antibodies, the presence of which favors localization of bacteria. While the problem is obviously a complex one, it would seem that further immunologic study might aid in the interpretation of the low incidence of syphilitic valvular disease complicated by bacterial endocarditis. Once bacteria become entangled in platelet thrombi, the immunologic factor appears to assume secondary importance.

Bacterial Endocarditis and Syphilitic Aortitis per Se—In recent years much confusion has arisen in the literature concerning the development of bacterial endocarditis in patients with syphilitic aortitis without syphilitic involvement of the aortic cusps and commissures. Most authors have inferentially regarded this combination as rare. In a large measure, this deduction has resulted from the failure to distinguish this combination from that of bacterial endocarditis engrafted on

42 Leary, T. Early Lesions of Rheumatic Endocarditis, *Arch. Path.* **13** 1 (Jan) 1932.

43 Mallory and Keefer, cited by Keefer³².

44 Grant, R. T., Wood, J. E., and Jones, T. D. Heart Valve Irregularities in Relation to Subacute Bacterial Endocarditis, *Heart* **14** 247 (Aug) 1928.

45 Friedman, M., Katz, L. N., and Howell, K. Experimental Endocarditis Due to *Streptococcus Viridans*. Biologic Factors in Its Development, *Arch. Int. Med.* **61** 95 (Jan) 1938.

syphilitic deformities of the aortic leaflets. Moreover, the erroneous impression conveyed by earlier writers has often been merely recapitulated but not subjected to critical inquiry. Thayer¹³ observed 2 instances of syphilitic aortitis in his series of cases of bacterial endocarditis of the aortic valve but justly disregarded the aortitis as a predisposing factor, for in the one instance, evidence of antecedent valvular disease was lacking, and in the other, the valvular defect was "in all probability" rheumatic in origin.

Skursky,¹⁷ François and Jouve,³⁰ Raybaud, Jouve and Farnarier²⁸ and Gallavardin and Gravier²⁷ stressed the rare occurrence of subacute bacterial endocarditis in patients with syphilitic aortitis per se but presented no statistical data. They recorded isolated instances to emphasize their contention. Raybaud and Jouve⁴⁶ reviewed the literature dealing with subacute bacterial endocarditis and syphilis and arrived at the same conclusion. However, they too failed to differentiate the instances of bacterial endocarditis complicating syphilitic valvular disease from those of bacterial endocarditis associated with syphilitic aortitis alone. Latterly, Smith,²⁴ in his review, reiterated the earlier opinions, stating that the "combination" of syphilitic aortitis and bacterial endocarditis is "decidedly rare," and reported 2 such cases. In the one, syphilitic aortitis was associated with acute endocarditis of the aortic valve due to *Staph aureus*, the aortic cusps being otherwise normal, in the other, it was associated with rheumatic aortic stenosis complicated by endocarditis of the aortic valve due to *Str viridans*. It is at once apparent that these cases differ materially from those constituting the subject of this paper and that a distinction must always be made.

From the present study it is evident that the concomitance of syphilitic aortitis and bacterial endocarditis is in reality not rare, since it was found in 19 instances in this series of 273 cases of bacterial (acute and subacute) endocarditis in which necropsy was done, an incidence of 7 per cent. In 7 of these 19 there was syphilitic valvular disease, and these 7 cases form the basis of this report. Of the remaining 12, in 4 the antecedent aortic valvular deformity was rheumatic in origin, in 4 the recent endocarditis did not develop on the aortic valves (3 on rheumatic mitral defects, 1 on a normal pulmonic valve), in 3 the nature of the earlier deformity of the aortic valves was not clear from the descriptions in the protocols, and in 1 the endocarditis had developed on coexisting congenital and syphilitic defects of the aortic cusps. Thus, in many instances, syphilitic aortitis may be but an incidental observa-

46 Raybaud, A., and Jouve, A. De la coexistence au niveau de la région sigmoïdienne aortique de lésions syphilitiques anciennes et d'une endocardite maligne à évolution lente ou subaigue, *Ann de méd* 39 211 (Feb) 1936

tion in the course of bacterial endocarditis, bearing no relationship to its development. Singularly illustrative of this, is an instance (case 741, 1934) in which the syphilitic changes in the aorta extended to the commissures, yet the lesions of subacute bacterial endocarditis had developed on a preexisting rheumatic aortic stenosis. As a corollary to this, it becomes clear that diagnosis on the basis of necropsy evidence alone should be regarded as conclusive and that syphilitic aortitis assumes importance as a possible predisposing factor to bacterial endocarditis only when the syphilitic process has extended to produce a deformity of the aortic valve.

Diagnosis—The clinical recognition of syphilitic aortic valvular disease, when complicated by bacterial endocarditis, may be fraught with much difficulty, especially if the initial examination is performed after the endocarditis has become manifest. Of paramount importance is an appreciation of the vulnerability of syphilitic valves to subsequent bacterial endocarditis, however rarely this combination may be encountered. Accordingly, a conscious effort must be made to exclude syphilitic valvular disease in all patients exhibiting bacterial endocarditis with aortic insufficiency. Although age, per se, does not preclude syphilitic valvular disease, even in patients in the third decade of life, nevertheless, in persons under 35 years of age, the underlying disease is more likely to be rheumatic. A careful anamnesis with special reference to syphilis as well as to the most common predecessor of bacterial endocarditis, namely, rheumatism in its various forms, in conjunction with a comprehensive physical examination, is most essential. Signs of organic mitral stenosis, while at times indistinguishable from a Flint murmur, suggest the rheumatic type of aortic insufficiency, whereas an accentuated, ringing second aortic sound points to syphilis as a cause. As cardiovascular syphilis is frequently accompanied by involvement of the central nervous system (an incidence as high as 54 per cent in the Mayo Clinic series, according to Stokes³⁷), the value of a carefully conducted neurologic study cannot be overemphasized. Pupillary and reflex changes, in particular, may direct attention to the possibility of underlying syphilis, and tests of the spinal fluid may provide confirmatory evidence. Indeed, in case 1 of the present series the diagnosis of syphilitic aortic insufficiency was first suspected from the absence of the achilles tendon reflexes coupled with the irregularity of the pupillary reflexes. But even in the presence of syphilis, aortic regurgitation may be due to simple dilatation of the aortic ring secondary to syphilitic aortitis rather than to valvular deformity or to an antecedent rheumatic or congenital disease (as already mentioned), and in such instances a correct clinical diagnosis along rational lines may not be possible.

The diagnostic significance of a positive Wassermann reaction in cases of subacute bacterial endocarditis merits more than passing comment. Landau and Held⁴⁷ reported positive reactions in 10 of 30 cases of endocarditis lenta. Of these 10 cases, 6 presented neither clinical evidence, nor a history, of syphilis, and in 4 of the 6 cases, no anatomic signs of syphilis were observed at necropsy. The positive reactions in these 6 cases were interpreted as incidental and secondary to a "disturbed colloid or lipid balance in the serum." Fulton and Levine²⁰ reviewed 111 clinical cases of subacute bacterial endocarditis, and, although in 9 there were positive Wassermann reactions, only 1 could be regarded as a case of syphilitic aortic insufficiency. Stokes⁸⁷ said that he had encountered at least 8 cases of strongly positive Wassermann reactions of the blood "with endocarditis manifestations, obviously of a septicemic or subacute bacterial type," and remarked that the occurrence of false positive serologic reactions in instances of subacute bacterial endocarditis may be accepted as established. He also alluded to the findings of E. Meyer,⁴⁸ who observed at the Goettingen Clinic 7 of 20 cases in which there were positive reactions. Wydrin⁴⁹ said that he concurred with this opinion but that he observed that of 50 cases of subacute bacterial endocarditis, in 4 there were positive reactions, and in only 1 of these were anatomic signs of syphilis lacking. Heilig⁵⁰ obtained positive reactions in 8 of 213 clinical cases of subacute bacterial endocarditis, and in none was there a history of syphilis. Grossman⁵¹ noted similar reactions in 4 of 21 cases, but no details were reported. These observations indicate that in the absence of syphilis a positive Wassermann reaction may occur occasionally in cases of this disease. Hence, should the patient state that he has never had syphilis and should a meticulous search reveal no signs of syphilis, the connotation of consistently positive reactions must be held in doubt. Perhaps other serologic tests, such as the Kahn and the Hinton test, together with the Wassermann test of the spinal fluid and the colloidal gold chloride test, may prove helpful.

As bacterial endocarditis more commonly attacks the rheumatic heart, it is necessary at necropsy to differentiate rheumatic from syphilitic aortitis, for the two may be confounded anatomically. From their

47 Landau, A., and Held, J. Sur la réaction de Bordet-Wassermann positive au cours de l'endocardite lente, *Bull. et mém. Soc. méd. d'hôp. de Paris* **49** 1322 (Oct. 9) 1925.

48 Meyer, E., cited by Stokes⁸⁷.

49 Wydrin, A. Bakteriämie, Wassermann-Reaktion und morphologisches Blutbild bei Endocarditis lenta, *Wien Arch. f. inn. Med.* **25** 231, 1934.

50 Heilig, F., cited by Wydrin⁴⁹.

51 Grossman, S., cited by Wydrin⁴⁹.

studies on the histologic changes in rheumatic aortitis, Klotz ⁵² and Pappenheimer and Von Glahn ⁵³ concluded that in syphilis the following conditions exist. The perivascular cellular infiltrations are greater, the scars are more extensive, many new capillaries are seen in the affected areas, and the intimal lesions are more frequent and more marked than in rheumatism. Further, in some cases of rheumatic aortitis, cellular infiltrations typical of, or resembling, Aschoff cells, may be seen (Pappenheimer and Von Glahn ⁵³) and, if present, may be regarded as of diagnostic value.

Finally, it is probable that with greater attention devoted to the condition of the aortic commissures one may find syphilis of the aortic valve and bacterial endocarditis coexistent more frequently than has hitherto been appreciated.

SUMMARY

The literature dealing with bacterial endocarditis and syphilitic valvular disease is critically reviewed, and the reported cases are grouped categorically as proved, doubtful and unproved.

Since Libman first directed attention to the infrequent concurrence of these diseases, only 10 proved cases have been reported. To these, the records of 7 more instances are added, making a total of 17 proved cases. Of the remaining cases in the literature, 4 are regarded as doubtful, and in 29 the existence of syphilitic aortic valvular disease remains unproved.

Based on the available data, a study of the incidence is made, and the suggestions offered for the interpretation of the rarity of this combination are discussed. Attention is drawn to the diagnostic difficulties and to the limitations of a positive Wassermann reaction.

Contrary to the opinions expressed in current literature, it is apparent from this study that bacterial endocarditis associated with syphilitic aortitis per se (without involvement of the aortic cusps or commissures) is not of rare occurrence.

With greater interest directed to the clinical and anatomic recognition of bacterial endocarditis superimposed on syphilitic valvular deformities, it is likely that their coexistence may be observed more frequently than heretofore.

The cooperation of Dr Otto Saphir was of valuable assistance in this study. Dr Walter Schiller gave permission for the study of the necropsy material at the Cook County Hospital.

⁵² Klotz, O. Rheumatic Fever and the Arteries, *Tr. A. Am. Physicians* 27: 181, 1912.

⁵³ Pappenheimer, A. M., and Von Glahn, W. C. Lesions of the Aorta Associated with Acute Rheumatic Fever and with Chronic Cardiac Disease of Rheumatic Origin, *J. M. Research* 44: 489 (Sept.) 1924.

SURVEY OF DIABETES

STATISTICAL DATA AND CONTROL COMPARISONS WITH
VARIOUS INSULINS

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LOS ANGELES

The data presented in this report are from the records of 800 diabetic patients who have been under our observation for one or more years. Laboratory analyses were performed at such intervals as would furnish reliable opinions regarding diabetic control. All of these patients are ambulatory. The series includes patients in our diabetic clinics for both adults and children, as well as private patients¹.

For convenience in arranging the mass of data from this number of records the patients have been divided into two groups, according to the nature of the onset of diabetes. Those who experienced the sudden onset of excessive thirst, polyuria and rapid loss of weight and strength before the diagnosis of diabetes was made are classed as having diabetes of acute onset. Patients who have had none of these symptoms in acute form at onset are classed as having diabetes of gradual onset. In the group with diabetes of gradual onset, the disease was discovered in routine insurance or health examinations or in a physical examination for some suspected disease other than diabetes. In both groups the patients are listed as juvenile when the onset of diabetes occurred while the patient was under 16 years of age.

The terms in all tables are defined as follows:

Severe diabetes	Diabetes requiring 40 units of insulin or more
Moderately severe diabetes	Diabetes requiring 20 to 40 units of insulin
Mild diabetes	Diabetes requiring 20 units of insulin or less

Based on diets containing 150 Gm. of carbohydrate

Good control	20 Gm. or less of sugar in urine in twenty-four hours
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¹ Clinic patients have been selected from the outpatient diabetic clinics of the Cedars of Lebanon Hospital and the Children's Hospital.

Fair control	20 to 40 Gm of sugar in urine in twenty-four hours
Poor control	40 Gm or more of sugar in urine in twenty-four hours
R-I	Regular amorphous insulin
ZP-I	Protamine zinc insulin
CZ-I	Crystalline zinc insulin

TABLE 1—*Classification of Patients with Diabetes of Gradual Onset*

Diabetes	Adult		Juvenile		Totals
	Gentiles	Jews	Gentiles	Jews	
Severe	12	1	4	0	17
Moderately severe	58	46	12	0	116
Mild	108	164	0	0	272
					405

TABLE 2—*Data on Patients with Diabetes of Gradual Onset*

Years Observed		Age at Onset	
1 to 2	43	0-9	6
2 to 3	65	10-19	10
3 to 4	56	20-29	16
4 to 5	55	30-39	56
5 to 10	146	40-49	134
10 to 15	28	50-59	112
15 to 20	9	60-69	62
20 to 25	3	70-79	9
	405		405

DIABETES OF GRADUAL ONSET

Of the total of 800 patients, 405 were found to belong in the group with diabetes of gradual onset. Of this number, only 16 were of juvenile age at onset. In table 1 it is shown that 67 per cent of the 405 patients with diabetes of gradual onset have a mild form of diabetes, and of these 60 per cent are Jewish. In table 2, with patients grouped as to age at onset, it is seen that in 60 per cent of the group with diabetes of gradual onset, diabetes was discovered between the ages of 40 and 60 years.

In 60 patients of the group with diabetes of gradual onset no organic disease was found in the routine examination that revealed glycosuria for the first time. All of these 60 patients have continued to show a mild

degree of diabetes In 98 patients the following conditions were present when diabetes was first found

	No of Patients
Organic cardiovascular disease	76
Carcinoma	3
Pyelitis, acute	5
Hypertrophy of prostate, benign	9
Hyperthyroidism	5
Hypothyroidism	4
Gallstones	7
Bronchial asthma	5
Pulmonary tuberculosis	5
Appendicitis, acute	7
Infection of upper respiratory tract, acute	13
Menopause	7
Pregnancy	5
Retinal arteriosclerosis, advanced	19
Furunculosis	6
Renal stone	1
Accident, with fracture	3
Syphilis	2
Spastic colitis	4
Mammary tumor, benign	3
Mastoiditis, acute	3
Tonsillitis, acute	3
Otitis media	2
Enteritis, acute	3
Bronchopneumonia	1
Measles	1
Mumps	1

In these 98 patients the severity of the diabetes is in direct proportion to the continued severity of the complication found at onset The 19 patients who had advanced retinal arteriosclerosis at onset have shown a gradual increase in the severity of their diabetes during several years of observation, but insulin therapy has been prescribed in moderation These patients are of advanced age, with general arteriosclerosis, and require protective therapy

OBESITY

Of the 405 patients with diabetes of gradual onset 247 were obese when glycosuria was first noted Private patients (133) averaged 37.9 pounds (17 Kg) above the normal weight, and clinic patients (114) averaged 53.3 pounds (24 Kg) above normal Of this group of 247 obese patients, 140 were Jewish and 107 gentiles Males numbered 83 and females 164 Eight patients were 100 pounds (45.4 Kg) or more above their normal weight, of these, 2 were males and 6 females In none of these cases of obesity was there found any cause of excess weight other than overeating Body weights recorded in January 1939 show an average loss of weight since onset of diabetes of 36.3 pounds (16 Kg) for 133 private patients and of 47.2 pounds (21 Kg) for 114 clinic patients In table 3 we present a comparison of the severity of diabetes in these obese patients at onset and at the time of writing The improvement shown in this table is proportionate to the loss of weight Of the 247 obese patients, 136 have required insulin Of this number, only 30 have stopped taking insulin and maintained full diabetic control on diet alone However, there are 52 patients who continue to take

insulin once daily in doses of 4 to 8 units, and this has been continued only as an aid to better cooperation for further loss of weight

Of the 405 patients with diabetes of gradual onset, 225 have required insulin. Of this number, 76 have been able to stop using insulin and have maintained good diabetic control on diet alone. Table 4 is a comparative study of control with the various forms of insulin. Of 225 patients treated with insulin, 158 began with the regular amorphous insulin, 55 began with protamine zinc insulin alone, 5 patients taking two injections daily, 2 patients began with a combination of regular and protamine zinc insulin, both taken each morning, and 10 patients began with crystalline zinc insulin, taking two injections daily. Patients

TABLE 3—*Effect of Loss of Weight on Two Hundred and Forty-Seven Obese Diabetic Patients*

Diabetes at Onset		Diabetes at Present	
Severe	0	Severe	0
Moderately severe	79	Moderately severe	32
Mild	168	Mild	215

TABLE 4—*Comparative Control with Various Insulins (Two Hundred and Twenty-Five Patients with Diabetes of Gradual Onset)*

Diabetes	R-I Control		ZP I Alone		R I and ZP I		CZ I Alone		CZ I and ZP I	
Severe	Good	11	Good	0	Good	6	Good	5	Good	4
	Fair	3	Fair	4	Fair	6	Fair	1	Fair	2
	Poor	8	Poor	1	Poor	5	Poor	0	Poor	0
Moderately severe	Good	44	Good	17	Good	12	Good	14	Good	7
	Fair	18	Fair	19	Fair	5	Fair	2	Fair	0
	Poor	14	Poor	22	Poor	5	Poor	0	Poor	0
Mild	Good	42	Good	68	Good	2	Good	34	Good	0
	Fair	12	Fair	32	Fair	1	Fair	0	Fair	0
	Poor	6	Poor	3	Poor	0	Poor	0	Poor	0

maintaining good diabetic control with any insulin were not changed to another insulin unless there was need for fewer injections or a change was requested for purposes of insulin study. At present 96 patients using protamine zinc insulin alone and 28 of the 34 mildly diabetic patients using crystalline zinc insulin alone are able to maintain full diabetic control with one daily injection. The 13 patients (table 4) receiving both crystalline and protamine zinc insulin have been most difficult to hold in moderate control with regular insulin and with regular insulin and protamine zinc insulin combined. At present these patients are taking both insulins in morning injections.

DIABETES OF ACUTE ONSET

Of the 800 patients, 395 had an acute onset of excess thirst, polyuria and rapid loss of weight and strength before the diagnosis of diabetes was made. These symptoms were severe in all of the 395 patients and

were given as the reason for the requested examinations in which diabetes was discovered. The interval between the onset of symptoms and the diagnosis of diabetes ranged from a few hours to several months. Longer delays in diagnosis caused many of the patients of this group to be first examined when in extreme ketosis and coma. However, the experience of the last few years indicates that an earlier diagnosis of diabetes is being made, with a marked decrease in the number of new patients who are first seen in coma.

Of the 395 patients with diabetes of acute onset, only 2 were overweight at onset. Twenty patients of this group have never required insulin, and 1 of these was of juvenile age at the time of onset. Only

TABLE 5—*Classification of Patients with Diabetes of Acute Onset*

Diabetes	Adult		Juvenile		Totals
	Gentiles	Jews	Gentiles	Jews	
Severe	33	21	62	17	133
Moderately severe	73	38	78	5	194
Mild	31	28	8	1	68
					395

TABLE 6—*Data on Patients with Diabetes of Acute Onset*

Years Observed	Adult	Juvenile	Age at Onset	
1 to 2	16	19	0-9	95
2 to 3	22	21	10-19	83
3 to 4	26	23	20-29	61
4 to 5	36	32	30-39	54
5 to 10	58	46	40-49	57
10 to 15	44	21	50-59	33
15 to 20	21	9	60-69	6
20 to 25	1			
	224	171		395

17 per cent of our 395 patients in the group with diabetes of acute onset had a mild degree of diabetes, and of the 224 patients who were of adult age at the time of onset 61 per cent were gentiles. Since the adult clinic is in the outpatient department of a Jewish hospital, this is of interest. Of the patients with diabetes of acute onset, 46.5 per cent were within the first two decades of life at the time of onset. The great majority of this group have diabetes which is severe or is in the more severe range of moderately severe.

Patients of the group with diabetes of acute onset who were of adult age at the time of onset have continued to manifest an acute clinical picture through years of close observation. Marked change in the control may follow very slight changes in diet or in the use of insulin, mild acute infections, nervous and emotional disturbances or changes in physical activity. As would be expected, the great majority of the

diabetic patients who have presented difficult problems in satisfactory and even control belong to the group with diabetes of acute onset

In the adult group represented in table 7, 174 patients began with the regular amorphous form of insulin, 17 began with protamine zinc insulin alone, 6 began with combined regular and protamine zinc insulins, 7 began with crystalline zinc insulin alone, and 1 began with combined crystalline zinc and protamine zinc insulins

In the juvenile group represented in table 8, 139 patients began with insulin of the amorphous form, 17 began with protamine zinc insulin

TABLE 7—*Comparative Control with Various Insulins (Two Hundred and Five Adult Patients with Diabetes of Acute Onset)*

Diabetes	R I Control		ZP I Alone		R-I and ZP I		CZ I Alone		CZ I and ZP I	
Severe	Good	12	Good	2	Good	14	Good	14	Good	26
	Fair	18	Fair	7	Fair	17	Fair	8	Fair	18
	Poor	10	Poor	12	Poor	9	Poor	0	Poor	1
Moderately severe	Good	27	Good	12	Good	24	Good	11	Good	21
	Fair	48	Fair	10	Fair	22	Fair	2	Fair	4
	Poor	26	Poor	15	Poor	15	Poor	0	Poor	0
Mild	Good	18	Good	14	Good	21	Good	18	Good	6
	Fair	10	Fair	1	Fair	1	Fair	0	Fair	0
	Poor	5	Poor	1	Poor	0	Poor	0	Poor	0

TABLE 8—*Comparative Control with Various Insulins (One Hundred and Seventy Juvenile Patients with Diabetes of Acute Onset)*

Diabetes	R-I Control		ZP I Alone		R I and ZP I		CZ I Alone		CZ I and ZP I	
Severe	Good	15	Good	3	Good	21	Good	5	Good	24
	Fair	22	Fair	7	Fair	23	Fair	0	Fair	18
	Poor	35	Poor	8	Poor	23	Poor	0	Poor	2
Moderately severe	Good	23	Good	6	Good	16	Good	4	Good	28
	Fair	27	Fair	4	Fair	11	Fair	0	Fair	0
	Poor	12	Poor	13	Poor	6	Poor	0	Poor	0
Mild	Good	5	Good	2	Good	0	Good	0	Good	0
	Fair	0	Fair	2	Fair	0	Fair	0	Fair	0
	Poor	0	Poor	0	Poor	0	Poor	0	Poor	0

alone, 6 began with combined regular and protamine zinc insulins, 7 began with crystalline zinc insulin alone, and 1 began with combined crystalline zinc and protamine zinc insulins. As with the patients of the group with diabetes of gradual onset who are taking insulin, none of the patients in the group with diabetes of acute onset were changed from any form of insulin that gave good control unless the convenience of fewer injections was of importance or insulin studies were requested. Only a few of the juvenile group with diabetes of acute onset have been observed while taking crystalline zinc insulin alone for sufficient time to be included in this report.

The records of 50 adult and 50 juvenile patients have been selected for comparison. These are among the more severely diabetic patients

of the group with diabetes of acute onset. Control comparisons were made with regular insulin, regular and protamine zinc insulins combined and crystalline zinc and protamine zinc insulins combined. The combined insulins were given in the morning only, but by separate injections. In table 9 are shown the degree of control with the various changes and the change in the unit dose of insulin required. The change in the unit dose of regular insulin and protamine zinc insulin combined is compared with that required with regular insulin alone. The daily unit dose of combined crystalline zinc and protamine zinc insulins is compared with that required with combined regular and protamine zinc insulins.

In tables 7 and 8 one sees a definite change in control toward good and fair degrees with combined regular and protamine zinc insulins.

TABLE 9—*Effect of Changes in the Type of Insulin Used (Fifty Adult and Fifty Juvenile Patients)*

		R-I and ZP-I						CZ-I and ZP-I			
		R I		Control		Dose		Control		Dose	
Adults	Diabetes	Control									
	Severe	Good	0	Good	11	Decreased	5	Good	14	Decreased	16
		Fair	14	Fair	8	Same	9	Fair	9	Same	8
		Poor	10	Poor	5	Increased	10	Poor	1	Increased	0
	Moderately severe	Good	0	Good	8	Decreased	5	Good	25	Decreased	22
		Fair	0	Fair	12	Same	5	Fair	1	Same	4
Poor		26	Poor	6	Increased	16	Poor	0	Increased	0	
Children	Severe	Good	0	Good	5	Decreased	1	Good	20	Decreased	23
		Fair	8	Fair	16	Same	7	Fair	11	Same	6
		Poor	24	Poor	11	Increased	24	Poor	1	Increased	3
	Moderately severe	Good	0	Good	1	Decreased	2	Good	11	Decreased	8
		Fair	8	Fair	10	Same	5	Fair	6	Same	4
		Poor	10	Poor	7	Increased	11	Poor	1	Increased	6

This becomes more satisfactory after a change to the crystalline form, either alone in two daily doses or in combination with protamine zinc insulin, with both insulins taken in the morning. Protamine zinc insulin used alone, in either one or two injections daily, has not been satisfactory in our experience except with mild diabetes or the milder range of moderately severe diabetes. The improved control secured with the change to crystalline zinc insulin or to combined crystalline zinc and protamine zinc insulins is even more satisfactory than can be shown by tabulation, since the cases in which the different insulin changes have been carried through have always presented the more difficult problems. An additional point in an estimation of improvement of diabetic control is shown in table 9, under the unit requirement of insulin for each form. In this table the unit dose has been given as the total number of units for the two forms of insulin used. Control with regular insulin alone requires three and often four injections of insulin daily for most of the adult and all of the juvenile patients in the selected group. With a

change to combined regular and protamine zinc insulins there is observed an improved control, with an increase in the number of patients in the "fair" and "good" grades. However, this improvement is seen to have been obtained by an increase in the dose of insulin, in a majority of the cases in the group. Efforts to improve control by giving protamine zinc insulin each morning and regular insulin either in the morning and at noon or in the morning and in the evening have not brought about any satisfactory change.

With crystalline zinc and protamine zinc insulins given each morning there is a definite improvement in control, with an associated decrease in the total unit requirement of insulin. The increases in units of insulin when combined regular and protamine zinc insulins are used are found to be mainly increases in unit dose of the protamine zinc form. Also, decreases in the unit dose of insulin when combined crystalline zinc and protamine zinc insulins are used are largely decreases in the dose of the protamine zinc form. This indicates some fault in the duration of effect of at least one form of insulin when two forms were combined.

Information in regard to the duration of the effect of insulin (regular, crystalline zinc and protamine zinc forms) was desired for clinical application especially to the problems indicated in table 9, in which the increases in unit dose of protamine zinc insulin were entirely out of proportion to those of regular insulin. Studies of the blood sugar were planned to include crystalline zinc insulin, with the same general technic that was followed in studies with precipitated insulins in 1936.²

ONSET AND DURATION OF THE EFFECT OF INSULIN AS MEASURED BY THE LEVEL OF BLOOD SUGARS

The composite graph (chart 1) shows the onset and duration of effect measured by the averaged values for blood sugar obtained from the 20 patients studied with three forms of insulin. With the morning dose of the amorphous form of insulin the patient loses the effect soon after noon. Consequently, patients with severe diabetes do not remain under insulin control through the afternoon when such control depends on a morning injection of regular insulin. An effect from the morning

2 Twenty patients with severe diabetes of acute onset were hospitalized for study. No changes were made in the diets except that all patients were given 15 Gm of carbohydrate as a midnight feeding. Adjustment periods of at least one week were allowed before each test day, and at least moderate diabetic control was secured during this time, usually by the aid of regular insulin. On test days, "micro blood sugars" were obtained before the morning insulin was given, thirty and sixty minutes after breakfast and each hour afterward until an uncontrolled rise in the level of blood sugar indicated loss of the effect of insulin. All insulin on the test days was given thirty minutes before breakfast and in the unit dose estimated as the requirement for each patient from observations made in the adjustment period.

dose of protamine zinc insulin is not obtained until late in the afternoon but continues from the time of onset throughout the night, terminating on the average at 6 a m, which is nearly twenty-four hours after the insulin was injected. It would seem probable (chart 1) that the use of regular and protamine zinc insulins, both taken in the morning, fails to supply insulin during the afternoon hours. The result of this blank period is an increase of glycosuria and hyperglycemia in the severely diabetic patient. The unit dose of protamine zinc insulin is expected to correct the afternoon disturbance and furnish available insulin for the entire night. This leads to an increase in unit dose of the slowly acting insulin that is much greater than what should be needed for the twelve hours of the night.

The curve in chart 1 shows that a morning dose of crystalline zinc insulin has an effect at onset that is nearly as early as that of amorphous insulin and endures into the late afternoon, terminating on the average at 4 p m. With our small group of severely diabetic patients crys-

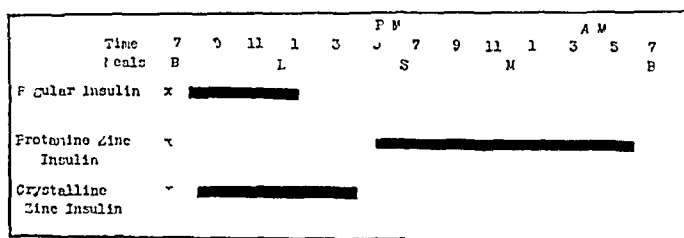


Chart 1—Onset and duration of the effect of insulin as measured by determination of the level of sugar in the blood. The time of injection of insulin, is represented by X, B represents breakfast, L, luncheon, S, supper, M, mid-night feeding.

talline zinc insulin gives control through the day up to one hour of the time of a beginning supply of insulin from the protamine zinc form. This should enable insulin from the slowly acting form to become available when diabetic control is better maintained, and the excess unit doses of protamine zinc insulin should not be required.

Chart 2 shows curves for the average blood sugar levels in the 20 patients taking regular and crystalline zinc insulins. The evidence of beginning effect of insulin with these two preparations is nearly the same in time, with an average of thirty minutes' delay with the crystalline form. The curve with regular insulin shows a more rapid depression of the level of blood sugar during the second and third hours after breakfast than is obtained with crystalline zinc insulin. The maximum depression of the concentration of blood sugar from the amorphous insulin was observed six and one-half hours after injection of regular

insulin and nine and one-half hours after injection of crystalline zinc insulin. For the small group with severe diabetes crystalline zinc insulin furnished available insulin three hours longer than did regular insulin (for an average of 20 cases). In none of the 20 patients studied was there found any complication that might affect the duration of the effect (during the period of observation in the hospital). The range in termination of insulin control for the crystalline zinc form was found to be from one to four hours longer than for the regular amorphous insulin.

COMMENT

The 800 patients included in this report were found to be equally divided into those with diabetes of acute onset and those with diabetes

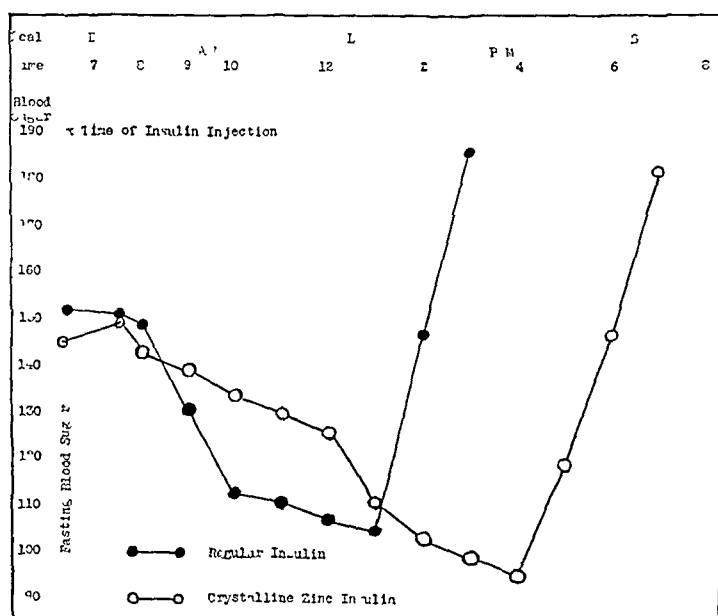


Chart 2—Blood sugar curves after administration of regular insulin and of crystalline zinc insulin. B, breakfast, L, luncheon, S, supper.

of gradual onset. Many of these patients have been under our observation for several years, and the majority of the juvenile group have been under our care since the onset of their diabetes. No claims are made for the significance of the grouping, but some contrasts between the two groups direct attention to the importance of the nature of the onset in all diabetic history taking. Patients previously reported as giving clinical evidence of sensitiveness to insulin are all included in the group with diabetes of acute onset. Patients of this group, even though the onset occurred at adult age, continue to show an acute response to slight changes in diet or insulin routines. Exaggerated loss of diabetic control

may result from mild complications For the total of 800 patients, the data on the two groups show the following contrasts

	Acute Onset (395 Patients)	Gradual Onset (405 Patients)
Number overweight at onset	2	247
Number not requiring insulin	20	180
Mild diabetes	17%	67%
Age of onset by decades	1 and 2, 46 6%	4 and 5, 60 7%
Ketosis	Frequent	Rare
Number juvenile at onset	171	16
Per cent Jewish	27 8%	52%
Clinical course	Always acute	Acute episodes rare

In the tables depicting control it is shown that slowly acting insulin has given good results in those patients who have mild diabetes The insulin requirement of these patients is moderate, and they usually maintain complete control with one morning injection of protamine zinc insulin Patients whose condition is in the milder range of moderately severe diabetes were usually unable to maintain good diabetic control on one daily injection of the precipitated insulin Two daily doses of crystalline zinc insulin gave control that was better maintained than that obtained with two daily injections of the amorphous insulin (when the crystalline zinc form was given at an interval of eleven to twelve hours) With evenly maintained control, improvement is manifested as a lengthening of duration of the effect of insulin, and a number of the patients have become listed as mildly diabetic and maintain full diabetic control on a morning dose of the crystalline zinc form alone

Selection of an insulin routine for patients with severe acute diabetes often requires a period of strict observation Recognition of any complicating disease is of great importance Knowledge of home and business environments must be obtained, and the nervous and emotional stability of each patient must be considered None of our patients with severe diabetes were able to maintain satisfactory control on protamine zinc insulin alone Insulin is not available long enough to furnish continued control from one daily injection When it is taken twice a day, there have resulted periods of severe shock, with the extreme and erratic symptoms peculiar to the persisting hypoglycemia from protamine zinc insulin These seem to result from the prolonged effect of this form of insulin, with overlapping periods during which excess insulin is active A small number of the severely diabetic patients have been asked to take two daily injections of crystalline zinc insulin at a twelve hour interval This has not given fully satisfactory control, but the results have been better than with precipitated insulin alone

Unless injections of insulin are to be taken at least twice daily, patients with severe diabetes present the problem of finding the form of insulin that gives an adequate and even insulin supply for the period in the twenty-four hours that is not covered by insulin from the protamine zinc form One morning dose of the slowly acting insulin, with regular

insulin taken morning and noon or morning and evening, has not given satisfactory and maintained control. While we are in full agreement that crystalline zinc insulin does not give the prolonged effect that is obtained with insulin derived from the protamine zinc preparation, we find that it is able to give protection for a few hours longer than can the amorphous insulin. This is particularly evident in cases of severe diabetes without complications that shorten the duration of effect of any available insulin. The more prolonged control (into the late afternoon) with a morning dose of crystalline zinc insulin together with control at night from protamine zinc insulin has given more satisfactory results (with a smaller unit requirement) than any routine we have tried.

All patients using insulin have been taught to make the injections into the subpannicular space. Patients in whom tender lumps or localized areas of redness have appeared at the site of injection have found that these will disappear with improvement in their technic of injection. Cutaneous tests for possible allergic sensitiveness have given negative results in every case with both protamine zinc and crystalline zinc insulins. Two patients had acute and severe spastic colitis within a few days after beginning to take protamine zinc insulin. The complication cleared when they returned to the amorphous insulin. Both had the same experience with crystalline zinc insulin. Cutaneous tests with zinc insulin combinations gave negative results. Both patients have moderately severe diabetes of acute onset, and both have been observed for twelve to fifteen years.

Four patients with moderately severe diabetes had been using crystalline zinc and protamine zinc insulins, taken each morning, for eight or more weeks. They were asked to change to the clear crystalline zinc form, with two injections daily. Several days after this change, these patients were found in severe insulin shock in the late hours of the night. The clinical picture and resistance of the condition was similar in each patient to hypoglycemia from the protamine zinc insulin, but there had been a period of three to ten days since any precipitated insulin had been taken. Patients who have had "insulin reaction" symptoms from the crystalline zinc form have had symptoms similar to those experienced with amorphous insulin, with rapid recovery. The possibility of incomplete absorption of insulin from the protamine zinc preparation, with late liberation of the "pocketed" insulin, could be a possible cause of the experience of the 4 patients.

Symptoms of "insulin reaction," with glycosuria and hyperglycemia, have been observed in past years with the amorphous insulin. These experiences were not frequent and were never severe. In the few years that zinc insulin combinations have been used, we have had several experiences with an extreme degree of this overcompensation with the

use of both forms of zinc insulin. Two patients, aged 11 and 67 years, both with moderately severe diabetes, were found deeply unconscious during the night. Both were noisy and wildly restless. The values for blood sugar were 368 and 400 mg per hundred cubic centimeters respectively when the patients were first seen. The older patient received dextrose intravenously, as oral feeding was not possible at first. Oral feedings were then carried out with both patients for twelve and sixteen hours, totals of 50 and 65 Gm of carbohydrate being given. Neither patient received any insulin, and both were fully conscious at the end of twelve and sixteen hours. The values for blood sugar were then found to be 16 and 42 mg per hundred cubic centimeters respectively.

Physical exercise appears to play an important role in the effectiveness of insulin of the crystalline zinc form. This has been manifested during the last year in patients of school and college age both with crystalline zinc insulin alone and with crystalline zinc and protamine zinc insulin taken in morning injections. It has been found necessary to reduce the unit dose of the crystalline zinc form as much as 10 units on the days when the patients are more than normally active. During the summer vacation, when the patients are at the seashore or in the mountains and unusually active, the same reductions are necessary.

All crystalline zinc insulin used in routine therapy is the product of Eli Lilly & Co or of Frederic Stearns & Company. That used in the studies reported here was supplied by Eli Lilly & Co.

Progress in Internal Medicine

INFECTIOUS DISEASES

A REVIEW OF SIGNIFICANT PUBLICATIONS IN 1939 1940

HOBART A REIMANN, M D

PHILADELPHIA

CHEMOTHERAPY

This year again, as in 1939, judging by the number of papers published on the subject, interest in chemotherapy dominates the field of infectious diseases. It is said that the incredible amount of 187 tons of sulfanilamide was used in the United States last year. Controlled experiments, too numerous to mention here, have in general confirmed earlier opinion as to the effectiveness or ineffectiveness of the sulfonamide derivatives in many diseases, in regard to others uncertainty still exists. In a recent review¹ are listed and discussed numerous infections for which both practical and experimental studies in man and in animals have shown the drugs to be of value, of doubtful value and of no value. There have also been many papers with overly enthusiastic conclusions from observations in single cases or in an insufficient number of uncontrolled therapeutic tests. The Council on Pharmacy and Chemistry of the American Medical Association has issued a revision of previous statements about both sulfanilamide and sulfapyridine² (2-[paraaminobenzenesulfonamido]-pyridine).

The mode of action of sulfanilamide, a matter of great importance, is still unknown. Numerous theories have been expressed. Locke and Mellon³ take exception to Shaffer's view of the ability of sulfanilamide to act as a reservoir for an intermediate substance of high oxidizing intensity, and to the claim that the toxic and the therapeutic effects have the same mechanism. The chemotherapeutic properties, they believe,

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1 Kolmer, J. A. Progress in Chemotherapy of Bacterial and Other Diseases, *Arch Int Med* **65** 671-743 (April) 1940. Heubner, W. Chemotherapie von Infektionskrankheiten, *Klin Wchschr* **19** 265-269 (March 23), 289-293 (March 30) 1940.

2 Sulfanilamide and Sulfapyridine, New and Nonofficial Remedies, *J. A. M. A.* **114** 326-327 (Jan 27) 1940.

3 Locke, A., and Mellon, R. R. The Mode of Action of Sulfanilamide, *Science* **90** 231-232 (Sept 8) 1939.

are to be sought in an active attack on the defense of the pathogen against peroxide, namely, against catalase, not on its defense against oxygen want. They postulate the stepwise formation of, first, a therapeutically active derivative and, second, a toxic derivative. Sulfanilamide, they reiterate, may produce only a retardation of the growth of pathogens susceptible to its action.

In another paper Mellon and McKinney,⁴ dealing with the pneumococcus, suggest that the accumulation of hydrogen peroxide after sulfapyridine therapy induces a form of dissociation of this bacterium. This phasic dissociation is not of the usual "M, S, R" sequence but involves a dwarf and a "G" type of colony, which are engulfed by phagocytes and destroyed. Many previous studies, however, provide no evidence that recovery from infection depends on microbic dissociation.

Broh-Kahn⁵ does not agree that sulfanilamide is bacteriostatic only in the presence of oxygen. His findings are like those of Bliss and Long,⁶ who reported bacteriostasis occurring under anaerobic conditions as well. His experiments indicate that the mechanisms suggested by Locke and Shaffer are not the sole ones concerned.

Lockwood's⁷ theory is of particular interest because of its simplicity. He suggests that sulfanilamide interferes with the ability of certain bacteria to utilize assimilable nitrogen in the form of protein split products in serum and other body fluids and that the presence of peptone provides assimilable nitrogen in such excess that the drug no longer acts effectively. It is possible that the drug combines in some way with free amino nitrogen and renders it unsuitable as food material for bacteria. Such a theory may explain the failure of the drug to cause bacteriostasis of certain micro-organisms in pus or in traumatized wounds.

New compounds are constantly being made and tested. One of them, sulfathiazole (2-[sulfanilamido]-thiazole), causes less nausea and vomiting but is as effective in pneumococcic pneumonia as sulfapyridine.⁸ Another compound, sulfamethylthiazole (2-sulfanilamido-4-methylthiazole), was found to be more effective than others against the

4 Mellon, R. R., and McKinney, R. A. The Biologic Nature of Sulfapyridine's Bacteriostatic Effect Against the Pneumococcus, *Proc. Soc. Exper. Biol. & Med.* **42** 677-679 (Dec.) 1939.

5 Broh-Kahn, R. H. The Bacteriostatic Action of Sulfanilamide Under Anaerobic Conditions, *Science* **90** 543-544 (Dec. 8) 1939.

6 Bliss, E. A., and Long, P. Observations upon the Mode of Action of Sulfanilamide and Sulfapyridine, abstracted, Report of the Proceedings of the third International Congress for Microbiology, New York, Sept. 2-9, 1939, New York, The Congress, 1940, pp. 585-586.

7 Lockwood, J. S., and Lynch, H. M. Studies on the Mechanism of the Action of Sulfanilamide, *J. A. M. A.* **114** 937-940 (March 16) 1940.

8 Long, P. H. Thiazole Derivatives of Sulfanilamide, *J. A. M. A.* **114** 870-871 (March 9) 1940.

staphylococcus, especially in test tube experiments⁹ Clinical trials are not yet numerous enough for one to judge its practical value In tissue culture studies Osgood¹⁰ found neoarsphenamine in high dilution to be far more effective than sulfapyridine against a variety of gram-positive cocci

Bauer and Rosenthal¹¹ show that the sulfur is apparently not essential to chemotherapeutic action Compounds active against streptococci were made by substituting arsenic or phosphorus for sulfur

Chemotherapy in Pneumonia—Without critical thought, a glance at a recently published chart¹² of mortality from pneumonia, which shows a strikingly low death rate from pneumonia in 1938-1939 as compared with 1928-1929, might be taken to indicate a triumph of chemotherapy If, however, similarly gathered statistics¹³ of other recent years are examined, the "pneumonia death rate [was] at a record low" in 1937-1938 Beginning in August 1937, every month except two showed a lower mortality rate from pneumonia than did the same month in any other year since 1920 According to another statistical report by the United States Bureau of Census,¹⁴ the mortality rate from "influenza and pneumonia" dropped from 207 per hundred thousand in 1900 to 114 per hundred thousand in 1937 The period covered by these statistics, of course, was before chemotherapy for pneumonia was available The increasing use of serotherapy may have played a role, but hardly enough to account for so great a reduction in mortality Before the important factors in lowering the death rate can be discovered it is necessary to know the morbidity rate of the disease If the morbidity rate is stationary and the mortality rate reduced as much as stated, there is reason to acclaim the success of specific therapy Accurate figures, unfortunately, are not available A significant fact is that in one

9 Barlow, O W, and Hamburger, E Specific Chemotherapy of Experimental Staphylococcus Infections with Thiazole Derivatives of Sulfanilamide, *Proc Soc Exper Biol & Med* **42** 792-795 (Dec) 1939

10 Osgood, E E Effectiveness of Neoarsphenamine, Sulfanilamide, Sulfapyridine in Marrow Cultures with Staphylococci and Alpha Streptococci, *Proc Soc Exper Biol & Med* **42** 795-799 (Dec) 1939

11 Bauer, H, and Rosenthal, S M Studies in Chemotherapy XI Antibacterial Action of Phosphorus Compounds, Preliminary Report, *Pub Health Rep* **54** 2093-2095 (Nov 24) 1939 Rosenthal, S M Experimental Chemotherapy with Sulfanilamide and Related Compounds, *J A M A* **113** 1710-1714 (Nov 4) 1939

12 Seasonal Incidence of Pneumonia Greatly Reduced, *Statist Bull Metrop Life Ins Co* **21** 7-8 (Feb) 1940

13 Pneumonia Death Rate at Record Low, *Statist Bull Metrop Life Ins Co* **19** 6-8 (Sept) 1938

14 Major Causes of Death, Increase in Life Expectancy and Population Changes in the United States, *Pub Health Rep* **54** 2054-2064 (Nov 17) 1939

study¹⁵ it was found that a drop of 27 per cent in mortality occurred in the first quarter of 1940 as compared with the same period in 1939

It is probable that numerous factors are at play. In the control of typhoid fever, for example, increased knowledge, specific vaccine, improved sanitation, improved diet, control of carriers and other measures all combined to reduce the incidence. Similar factors were operative against tuberculosis. The lowest death rates in history were recently recorded¹⁵ for diarrheal diseases, appendicitis and puerperal conditions. Whether or not serotherapy and chemotherapy are alone responsible for the recent lowering of the death rate in pneumonia, or whether the prevalence of this disease, like that of other diseases, is cyclic, and the present low ebb is merely a phase, only the future can tell. Whatever the cause, there is no doubt that the widespread use of chemotherapy and serotherapy, owing in part to the activities of numerous organized attempts to control pneumonia, can be expected to contribute to the advantage gained.

Indications are suggestive that unknown factors may also be operative. For example, in the experience of Reimann and Stokes¹⁶ with an infection of the respiratory tract in 1939, probably caused by a filtrable agent, pneumococci were surprisingly scarce. They were isolated from the sputum of only 8 of 100 patients. It is generally believed that from 35 to 50 per cent of normal persons carry pneumococci in the nasopharynx habitually, and mild infections of the respiratory tract supposedly increase this percentage. The paucity of pneumococci in our own recent experience¹⁶ may indicate a temporary diminution in their numbers and prevalence in certain localities as a result of influences totally unknown.

Except for confirmation of early reports, not much new information has accumulated as to the value of sulfapyridine in pneumococcal pneumonia. A bibliography of 122 references may be found in Marriott's paper¹⁷. A good review is also found in a paper by Long and Wood¹⁸. The consensus favors the use of chemotherapy but not to the exclusion of specific serum therapy. Chemotherapy seems to lower the mortality

15 Mortality Experience of the First Three Months of 1940. Sharp Drop in Deaths from Pneumonia, *Statist. Bull. Metrop. Life Ins. Co.* **21**: 8 (April) 1940.

16 Reimann, H. A., and Stokes, J., Jr. An Epidemic Infection of the Respiratory Tract in 1938-1939. A Newly Recognized Entity, *Tr. A. Am. Physicians* **54**: 123-127, 1939. Reimann, H. A., and Havens, W. P. An Epidemic Disease of the Respiratory Tract, *Arch. Int. Med.* **65**: 138-150 (Jan.) 1940.

17 Marriott, H. L. Sulphapyridine (M & B) 693 and Pneumococcal Infections, *Brit. M. J.* **2**: 944-947 (Nov. 11) 1939.

18 Long, P. H., and Wood, W. B. Observations upon the Experimental and Clinical Use of Sulfapyridine. II. The Treatment of Pneumococcal Pneumonia with Sulfapyridine, *Ann. Int. Med.* **13**: 487-512 (Sept.) 1939.

rate in pneumococcic pneumonia to about 55 per cent, according to Marriott, who summarizes the collective results in 1,991 treated patients. On the other hand, surprisingly low mortality rates of 23 per cent and 44 per cent following serotherapy have been reported¹⁹. Dowling and Abernethy²⁰ record a mortality rate of 14 per cent among 70 serum-treated patients and a rate of 96 per cent among those treated with sulfapyridine but do not believe that it is possible to judge the relative merits of either form of treatment yet. Aside from these figures there is at present no evidence to prove the superiority of one form of treatment over the other²¹. Unless work to decide this question is carefully controlled, inaccurate conclusions may be drawn. For example, it is highly probable that serum, because of the trouble and expense of giving it, is administered only to patients who are severely ill, while sulfapyridine is certainly used more indiscriminately. If many patients who are "suspected" of having pneumonia or who suffer from a condition erroneously considered to be pneumonia are included in statistics as drug-treated patients, the mortality rate will indeed be low.

Few physicians in actual practice will continue to use serotherapy, with its complicated details and expense, in preference to the simpler method of giving a few pills if the latter will yield equally good or better results and if the number of hazards is about the same. Several authorities advise chemotherapy alone in the average case but include specific immune serum when (a) sulfapyridine has been given for eighteen to twenty-four hours without improvement, (b) the patient is over 40 years of age, (c) the patient is pregnant or in the early puerperium, (d) more than one lobe is involved, and (e) the blood culture is positive.

In numerous states, particularly in New York, Massachusetts and Illinois, excellent brochures on the treatment of pneumonia have been prepared for free distribution by committees for the control of pneumonia. Unfortunately in some of them, as well as in current comment²² and in a query,²³ sulfapyridine therapy is recommended as soon as a diagnosis

19 Loughlin, E. H., Bennett, R. H., and Spitz, S. H. The Treatment of Types V, VII and VIII Pneumococcal Pneumonias with Rabbit Antipneumococcus Serum, *New York State J. Med.* **39** 1713-1721 (Sept. 15) 1939. Callomon, V. B. Treatment of Pneumonia with Type Specific Rabbit Serum, *Am. J. M. Sc.* **198** 349-356 (Sept.) 1939.

20 Dowling, H. F., and Abernethy, T. J. Treatment of Pneumococcic Pneumonia. Comparison of Results Obtained with Specific Serum and with Sulfapyridine, *Am. J. M. Sc.* **199** 55-62 (Jan.) 1940.

21 Comparative Value of Serum Therapy and Chemotherapy in Pneumococcic Pneumonia, editorial, *J. A. M. A.* **114** 662-663 (Feb. 24) 1940.

22 Treatment of Pneumonia, Current Comment, *J. A. M. A.* **113** 2324 (Dec. 23) 1939.

23 Sulfapyridine Contraindicated in Prophylaxis of Pneumonia, Queries and Minor Notes, *J. A. M. A.* **114** 1689 (April 27) 1940.

of pneumonia is made. This recommendation, I believe, is too broad, the application of this drug should be restricted to clinical lobar pneumonia, or better still to pneumonia caused by the pneumococcus or by the hemolytic streptococcus, and perhaps the staphylococcus. There are many forms of pneumonia for which the drugs available are of no value. Blake and Haviland,²⁴ and the discussers of their paper, point out the ineffectiveness of sulfapyridine in pneumonia not caused by the pneumococcus. Furthermore, according to Brown and his co-workers²⁵

The range between adequate blood concentration [of sulfapyridine] and those which carry an unwarrantable risk of serious toxicity has been shown to be so narrow as to provide justification for a more conservative approach to the chemical treatment of pneumonia and to constitute a valid argument against the indiscriminate substitution of sulfapyridine for sulfanilamide in non-pneumococcic infections.

Except under unusual circumstances there is at present no logical basis for the use of the sulfonamide compounds as prophylactic against pneumonia in persons who have infections of the respiratory tract. If, as has been estimated, pneumonia develops in only 1 of every 1,000 persons with colds, the uselessness of small doses and the occasional toxic results of effective doses of the drugs now available do not justify the risk of drug poisoning.

I have repeatedly pointed out that chemotherapy must not be used indiscriminately for every patient who has fever and a few rales in the lung. The drugs now available have no beneficial effect on the influenza-like pulmonary disease of extremely low mortality which has been prevalent for several years. Nor are they indicated in pulmonary congestion or in mixed infections of the lungs in which pneumococci or hemolytic streptococci are not present, although they have apparently been of value in postoperative pneumonia.²⁶ I have recently seen a number of patients with sulfanilamide poisoning to whom the drug was given without previous attempt having been made to discover the cause of the pneumonia, which in each case was atypical. In such cases it often happens that if no beneficial effect is noted after a reasonable trial of the drug, instead of stopping its use, the physician gives more and more until poisoning results. It is just as important to know when not to use chemotherapy and when to stop using it, as it is to know

24 Blake, F. G., and Haviland, J. W. Sulfapyridine in Pneumococcal, Streptococcal and Staphylococcal Infections, *Tr. A. Am. Physicians* **54** 130-148, 1939.

25 Brown, W. H., Thornton, W. B., and Wilson, J. S. An Evaluation of the Clinical Toxicity of Sulfanilamide and Sulfapyridine, *J. A. M. A.* **114** 1605-1611 (April 27) 1940.

26 Hinshaw, H. C., and Moersch, H. J. Sulfapyridine in Treatment of Pneumonia with Special Reference to Postoperative Pneumonia, *Arch. Surg.* **39** 275-281 (Aug.) 1939.

when to use it Whitby²⁷ believes such drug poisoning to be a matter of misjudgment not so much as regards primary prescription of the drug but as regards stopping its use after a trial period of a few days has shown no clinical effect It would be important to learn whether many patients who supposedly die of an infection do not actually die from drug poisoning

In the treatment of pneumococcic pneumonia there is still some uncertainty as to the optimal level of sulfapyridine in the blood Some²⁸ believe that frequent measurements of the level have limited value, since many patients improve with 2 mg or less per hundred cubic centimeters of blood, others²⁹ believe that results are better if the level is kept at 6 mg per hundred cubic centimeters or higher In this case the newly introduced, more soluble sodium salt of sulfapyridine when injected intravenously seems to be of value in raising the level to the desired point more speedily³⁰ The intravenous injection of this compound is recommended when for some reason oral medication is difficult or impossible and when it is difficult to obtain a satisfactory amount in the blood Unfortunately, unpleasant side effects, such as nausea, may occur, as with oral therapy (Finland and his co-workers³¹)

There is also uncertainty as to the length of time sulfapyridine therapy should be kept up after apparent recovery from pneumonia Christian³² suggests stopping therapy as soon as the temperature drops, but Blake, Longcope, Blankenhorn and Cecil³² keep it up for several days after recovery, or approximately until the seventh or eighth day after the onset of the disease

During the past winter sulfathiazole was tested in the treatment of pneumonia^{32a} In our hands it was as effective as sulfapyridine and caused

27 Whitby, L E H The Use and Abuse of Chemotherapeutic Agents of the Sulphonamide Group, *Practitioner* **144** 1-4 (Jan) 1940

28 Pepper, D S, Flippin, H F, Schwartz, L, and Lockwood, J S The Results of Sulfapyridine Therapy in Four Hundred Cases of Typical Pneumococcic Pneumonia, *Am J M Sc* **198** 22 (July) 1939

29 Abernethy, R J, Dowling, H F, and Hartman, C R The Treatment of Lobar Pneumonia with Sulfapyridine and Sodium Sulfapyridine, with Observations upon Effective Blood Levels, *Ann Int Med* **13** 1121-1137 (Jan) 1940

30 Gaisford, W F, Evans, G M, and Whitelaw, W Parenteral Therapy with Sulphapyridine Soluble, *Lancet* **2** 69-71 (July 8) 1939

31 Finland, M, Lowell, F C, Spring, W C, and Taylor, F H L Parenteral Sulfapyridine The Intravenous Use of Sodium Sulfapyridine and a Report of Clinical and Laboratory Observations on the Use of a Glucose Sulfapyridine Solution, *Ann Int Med* **13** 1105-1120 (Jan) 1940

32 Christian, H A, Longcope, W T, Blankenhorn, M A, and Cecil, R L, in discussion on Blake and Haviland²⁴

32a Flippin, H S, Schwartz, L, and Rose, F B The Comparative Effectiveness and Toxicity of Sulfathiazole and Sulfapyridine in Pneumococcic Pneumonia, *Ann Int Med* **13** 2038-2049 (May) 1940

less nausea and vomiting Erythema appeared in a few cases The sodium salt of this compound is also effective when given intravenously

Favorable reports continue to appear about chemotherapy in pneumococcic meningitis Hodes and his co-workers³³ had success in 8 of 17 patients with this infection English observers record 2 unsuccessful results, the treatment failed in a patient with empyema,³⁴ and in another patient pneumococcic meningitis developed during treatment of pneumonia with sulfapyridine³⁵

Experimental Studies—Spring, Lowell and Finland³⁶ grew pneumococci in various concentrations of sulfapyridine and serum with the following results Growth of pneumococci usually occurred equally well up to four hours in mediums with and without sulfapyridine After this time the drug was bacteriostatic and bactericidal The degree of effect noted depended on the concentration of the drug and the number of pneumococci inoculated Growth always occurred before sulfapyridine exerted its effect The combination of small amounts of serum with sulfapyridine was even more effective in causing bacteriostasis than either agent used alone The presence of the specific soluble capsular substance did not reduce the efficiency of the drug

In a clinical study the same authors³⁷ again demonstrated the superiority of a combination of serum and drug over either used separately The bactericidal effect of specific immune serum was much more rapidly exerted than the bacteriostatic effect of the drug The results of Kneeland and Mulliken³⁸ indicate that in most patients with lobar pneumonia treated with sulfapyridine an excess of antibody does not appear It seems that the action of the drug on the bacteria lessens the need for antibodies, which are therefore not produced, because the stimulus is lacking The drug apparently supplements, at least to some degree, the immune mechanism

33 Hodes, H L , Gimbel, H S , and Burnett, G W Treatment of Pneumococcic Meningitis with Sulfapyridine and the Sodium Salt of Sulfapyridine, J A M A **113** 1614-1619 (Oct 28) 1939

34 Aitchison, J D Pneumococcal Meningitis Complicating Pneumococcal Empyema Treated Unsuccessfully with M & B 693, Lancet **1** 1436 (June 24) 1939

35 Dowds, J H Pneumococcal Meningitis Developing During Treatment with M & B 693, Lancet **1** 1436-1437 (June 24) 1939

36 Spring, W C , Lowell, F C , and Finland, M Studies on the Action of Sulfapyridine on Pneumococci, J Clin Investigation **19** 163-178 (Jan) 1940

37 Finland, M , Spring, W C , and Lowell, F C Immunological Studies on Patients with Pneumococcic Pneumonia Treated with Sulfapyridine, J Clin Investigation **19** 179-199 (Jan) 1940

38 Kneeland, Y , and Mulliken, B Antibody Formation in Cases of Lobar Pneumonia Treated with Sulfapyridine J Clin Investigation **19** 307-312 (March) 1940

The experience of others³⁹ in treating dogs experimentally infected with a strain of type I pneumococci is in accord with clinical reports of the curative property of sulfapyridine. The influence of the drug was evident even in far advanced disease, but, as in man, its effectiveness was limited in the presence of suppurative complications. The authors could not confirm the reports of certain investigators that pneumococci lose their capsules during therapy. Type-specific capsulated pneumococci were found in both blood and lung tissue.

In Streptococcal Infections—Sulfanilamide, according to Hoyne, Wolf and Prim,⁴⁰ is the most effective means of treatment of erysipelas. The fatality rate among 162 treated patients was 2.4 per cent, the lowest in their experience. Rantz and Keefer⁴¹ also write that the drug shortens the course of the infection if given within the first three days. Complications, however, were frequent, and recurrence and relapse occurred in spite of treatment.

Chemotherapy is not always successful against infections with the hemolytic streptococcus. In a boy whose blood contained 14.9 mg. of sulfanilamide while he was under treatment for otitis media caused by the hemolytic streptococcus, peritonitis developed, and later pneumonia with pericarditis.⁴² Such incidents support the view that chemotherapy alone is not always sufficient to overcome infection, an immune response from the host may also be necessary. The presence of pus inhibits bacteriostasis.

Patients with the usual forms of sore throat caused by the hemolytic streptococcus should not be given sulfanilamide unless serious complications, such as severe cervical adenitis, sinusitis, mastoiditis or meningitis, develop. In a controlled study, Rhoads and Afremow⁴³ show that the drug did not reduce the severity of tonsillitis, shorten its course, reduce the incidence of complications or reduce the duration of the carrier state. Sulfanilamide failed to check epidemics of scarlet

39 Gregg, L. A., Hamburger, M., and Loosli, C. G. Sulfapyridine in Experimental Pneumococcal Pneumonia in the Dog, *J. Clin. Investigation* **19** 257-265 (Jan.) 1940.

40 Hoyne, A. L., Wolf, A. A., and Prim, L. Fatality Rates in the Treatment of Nine Hundred and Ninety-Eight Erysipelas Patients, *J. A. M. A.* **113** 2279-2281 (Dec. 23) 1939.

41 Rantz, L. A., and Keefer, C. S. Sulfanilamide in the Treatment of Erysipelas, *New England J. Med.* **221** 809-813 (Nov. 23) 1939.

42 Botsford, T. W., and Lanman, T. H. Primary Streptococcal Peritonitis. Report of a Case Which Developed While the Patient Was Undergoing Sulfanilamide Therapy, *New England J. Med.* **221** 651-653 (Oct. 26) 1939.

43 Rhoads, P. S., and Afremow, M. L. Sulfanilamide in Treatment of Sore Throat Due to Hemolytic Streptococci, *J. A. M. A.* **114** 942-943 (March 16) 1940.

fever in an Australian hospital,⁴⁴ but small doses were given. Two children contracted scarlet fever associated with type II streptococci while under treatment.

One group of workers⁴⁵ report favorable results in the treatment of chronic ulcerative colitis. When one considers the unknown cause of the disease and the tendency toward spontaneous remission, the results seem unconvincing.

The British Royal Army Medical Corps⁴⁶ has issued a memorandum on the prophylaxis and treatment of war wounds likely to be infected with streptococci or gas-forming bacilli. Patients who have such wounds are to be given 4 Gm. of sulfanilamide at once, 2 Gm. four hours later, then 1 Gm. every four hours for ten days. Then if no benefit is apparent, sulfapyridine should be used. Subsequent studies⁴⁷ support the prophylactic use of drugs, but the authors recommend that 1.5 Gm. be given as soon as possible after the wound has been received, followed by doses of 0.5 Gm. each at four hour intervals for four days.

In Subacute Bacterial Endocarditis—Two more cases of apparent recovery from endocarditis after treatment with sulfanilamide are reported,⁴⁸ but Spink and Crago⁴⁹ report that of 11 patients only 2 seemed to be temporarily helped, and 1 of these died later. Reasoning that drugs cannot attack bacteria when these are buried deep in clots or vegetations on the cardiac valves, other investigators⁵⁰ gave patients sulfanilamide and heparin. Heparin is supposed to prevent the formation of fibrin clots and leave the streptococci unprotected against the drug. In our own experience and in that of others (unpublished) the

44 Keogh, E. V., McDonald, I., Battle, J., Simons, R. T., and Williams, S. Some Factors Influencing the Spread of Scarlet Fever in an Institution, *J. Hyg.* **39** 664-673, 1939.

45 Brown, A. E., Herrell, W. E., and Bagen, J. A. Neoprontosil (Oral) in Treatment of Chronic Ulcerative Colitis, *Ann. Int. Med.* **13** 700-710 (Oct.) 1939.

46 The Chemotherapy of Infected War Wounds, Foreign Letters, *J. A. M. A.* **113** 1251 (Dec. 16) 1939.

47 Fuller, A. T., and James, G. V. Dosage of Sulphanilamide in Prophylaxis of Wound Infections, *Lancet* **1** 487-490 (March 16) 1940.

48 Major, R. H., and Leger, L. H. Recovery from Subacute Bacterial Endocarditis, *J. Kansas M. Soc.* **40** 324-325 (Aug.) 1939. Heyman, J. Subacute Bacterial Endocarditis Successfully Treated with Sulfanilamide. Report of Well Established Case Eighteen Months After Recovery, *J. A. M. A.* **114** 2373-2375 (June 15) 1940.

49 Spink, W., and Crago, F. H. Evaluation of Sulfanilamide in the Treatment of Patients with Subacute Bacterial Endocarditis, *Arch. Int. Med.* **64** 228-248 (Aug.) 1939.

50 Kelson, S. R., and White, P. D. Treatment of Subacute Bacterial Endocarditis, *J. A. M. A.* **113** 1700-1702 (Nov. 4) 1939. Friedman, M., Hamburger, W. W., and Katz, L. N. Use of Heparin in Subacute Bacterial Endocarditis, *ibid.* **113** 1702-1703 (Nov. 4) 1939.

results of such treatment have been uniformly disappointing, especially in patients treated late in the disease. At the meeting of the American Society for Experimental Pathology in New Orleans, in March 1940, Gruhzt⁵¹ announced a new drug, paranitrobenzoate, which protects mice against *Streptococcus viridans*. In my experience this bacterium was never pathogenic for mice, and one wonders what technic was used to permit therapeutic tests to be made. No reports have been published as yet on the use of the drug in human patients.

In Staphylococcic Infections—Although Blake and Haviland²⁴ noted no benefit from sulfapyridine, others⁵² have reported several cases of bacteremia in which the drug was used, often together with many other measures, and the patients recovered. Single case reports concerning relatively common infections may mislead one to be prematurely enthusiastic about chemotherapy and would better be withheld until more comprehensive studies have been made. Furthermore, many physicians still regard "staphylococcic septicemia as almost invariably fatal"^{52a}. Such is not the case, the mortality rate without special therapy is about 60 per cent, so that any procedure may be wrongly credited with a 40 per cent cure rate. The prognosis is even more favorable in the case of children, and 3 of the 4 instances reported concerned children. British writers are also guilty of publishing reports of uncontrolled studies or of single cases,⁵³ and in one study⁵⁴ only 2 of 6 patients recovered. Many competent observers, however, are enthusiastic about the results in certain cases.

Hope may be had, however, for better success since two new compounds sulfamethylthiazole (2-sulfanilamido-4-methylthiazole) and sulfaphenylthiazole (2-sulfanilamidophenylthiazole) have been found to be more effective than previously used drugs against staphylococci in broth cultures⁵⁵. As might have been expected, a report^{55b} has already

51 Gruhzt, A. M. A New Approach in the Therapy of Septicemia Due to *Streptococcus Viridans* in Experimental Animals, abstracted, Arch Path **29** 732 (May) 1940.

52 (a) Thornhill, W. A., Swart, H. A., and Reel, C. Sulfanilamide in Staphylococcic Septicemia, J A M A **113** 1638-1639 (Oct 28) 1939. (b) Goldberg, S. L., and Sachs, A. Sulfapyridine in the Treatment of Staphylococcus Aureus Bacteremia, *ibid* **113** 1639-1641 (Oct 28) 1939.

53 Galewski, S., and Stannus, H. S. Septicemia Due to *Staphylococcus Albus* Treated with M & B 693, Lancet **2** 1067-1068 (Nov 18) 1939.

54 Abramson, A. W., and Flacks, B. Staphylococcal Septicaemia Complicating Carbuncle of the Face, Lancet **2** 1065-1067 (Nov 18) 1939.

55 (a) Lawrence, C. A. Bacteriostatic Actions of Three Thiazole Derivatives of Sulfanilamide upon Bacteria in Broth Cultures, Proc Soc Exper Biol & Med **43** 92-97 (Jan) 1940. (b) Herrell, W. E., and Brown, A. E. The Clinical Use of Sulfamethylthiazol in Infections Caused by *Staphylococcus Aureus*. Preliminary Report, Proc Staff Meet, Mayo Clin **14** 753-758 (Nov 29) 1939.

been published of a single case in which the drug supposedly had curative value. In one study⁵⁶ sulfathiazole was better than sulfamethylthiazole in experiments on mice, but the reverse was true in the test tube. The observers rightly point out how minor variations in the technic used can greatly influence the results. In another study⁵⁷ sulfathiazole was more effective than sulfapyridine. It may be of importance to use both drugs and specific immune serum⁵⁸ in combating staphylococcic infections.

In Peritonitis—Surgeons report a marked reduction of mortality from peritonitis after appendectomy in patients treated with sulfanilamide⁵⁹. The mortality rate among 552 patients before sulfanilamide was available was 1.5 per cent. In a subsequent group of 257 who were treated in the same way but received the drug in addition, the rate was 0.4 per cent. Unfortunately, alternate controls were not studied at the same time, a fact which considerably reduces the significance of this report. No special attempts were made, or recommended, toward discovering the causative bacteria.

In Gonococcic Infections—Fletcher and Scott⁶⁰ treated 4 patients for gonococcic endocarditis with sulfanilamide. Three died, and the diagnosis of the condition for the one who recovered was not fully proved.

Although sulfanilamide is regarded almost unanimously as the most effective treatment yet used in treating gonorrheal urethritis, relapses frequently occur. In one series of 1,005 patients at least 12 per cent had relapses⁶¹.

In Miscellaneous Conditions—The effect of sulfanilamide in tuberculosis is still controversial. Experiences of Follis and Rich⁶² with

56 Rake, G., and McKee, C. M. Action of Sulfathiazole and Sulfamethylthiazole on *Staphylococcus Aureus*, *Proc Soc Exper Biol & Med* **43** 561-564 (March) 1940.

57 Bliss, E. A., and Ott, E. Effect of Sulfapyridine, Sulfathiazole and Sulfamethylthiazol upon Some Staphylococcic Infections in Mice, *Proc Soc Exper Biol & Med* **43** 706-709 (April) 1940.

58 Julianelle, L. A. Observations on the Specific Treatment (Type A Antiserum) of Staphylococcal Septicemia, *Ann Int Med* **13** 308-316 (Aug.) 1939.

59 Ravdin, I. S., Rhoads, J. E., and Lockwood, J. S. The Use of Sulfanilamide in the Treatment of Peritonitis Associated with Appendicitis, *Ann Surg* **111** 53-63 (Jan.) 1940.

60 Fletcher, P. H., and Scott, V. C. Four Cases of Gonococcic Endocarditis Treated with Sulfanilamide with Recovery of One, *Bull Johns Hopkins Hosp* **65** 377-392 (Nov.) 1939.

61 Cockkins, A. J., and McElligott, G. L. M. Relapses After Sulfonamide Cure of Gonorrhea, *Brit M J* **2** 1080-1083 (Dec 2) 1939.

62 Follis, R. H., and Rich, A. R. Further Studies on the Effect of Sulfanilamide on Experimental Tuberculosis, *Bull Johns Hopkins Hosp* **65** 466-483 (Dec) 1939.

rabbits confirmed their previous observation that sulfanilamide in adequate doses and properly given has a definite inhibitory effect on the development of tuberculosis. Others⁶³ find that the drug has no effect on experimental tuberculous infection in guinea pigs. Sulfapyridine is slightly more effective than sulfanilamide *in vitro*, but sulfapyridine had no effect on tuberculosis in 7 patients⁶⁴.

Sulfapyridine was more effective than sulfanilamide in the treatment of an infection with Friedlander's bacillus in mice, but too few animals were used in the experiments reported⁶⁵ to render final judgment possible as to the value of the drug. One patient with septicemia due to Friedlander's bacillus was given sulfapyridine and recovered⁶⁶.

Too few mice were used to enable one to draw conclusions as to the effectiveness of sulfapyridine in experimental infection with *Bacillus coli*. An enthusiastic report of the beneficial effect of both sulfanilamide and sulfapyridine in the treatment of typhoid fever originated in England⁶⁷. Seven patients were treated with apparently good results. Good results were also apparently attained in 3 of 4 other patients treated with sulfathiazole^{67a}.

Success was reported⁶⁸ in treating an experimental infection with *Listerella* in mice. Sulfanilamide caused striking improvement in patients with chancroid⁶⁹.

63 Steimbach, M. M., and Dillon, B. M. Sulfanilamide in Experimental Tuberculosis, *Proc Soc Exper Biol & Med* **41** 613-616 (June) 1939. Birkhaug, K. Sulphonamide Treatment of Experimental Tuberculosis in Guinea Pigs, Bergen, Norway, A. S. John Griegs Boktrykkeri, 1939. Bacteriostatic Effect of Sulfapyridine, Sulfanilamide and Prontosil Rubium *In Vitro* on Mycobacteria, *Proc Soc Exper Biol & Med* **42** 275-277 (Oct) 1939.

64 Allison, S. T., and Myers, R. The Treatment of Pulmonary Tuberculosis with Sulfapyridine, *J A M A* **113** 1631-1634 (Oct 28) 1939.

65 Kolmer, J. A., and Rule, A. M. Sulfanilamide and Sulfapyridine in the Treatment of Experimental B. Friedlander (*Klebsiella Pneumoniae*) Infections of Mice, *Proc Soc Exper Biol & Med* **42** 305-307 (Oct) 1939.

66 Meyer, K. A., and Amtman, L. Treatment of Friedlander's Septicemia by Sulfapyridine with Recovery, *J A M A* **113** 1641-1642 (Oct 28) 1939.

67 Harries, E. H. R., Swyer, R., and Thompson, N. Sulfanilamide in Typhoid Fever, *Lancet* **1** 1321-1322 (June 10) 1939.

67a Weilbaecher, J. O., Moss, E. S., Taylor, H. N., and Duprey, H. The Treatment of Typhoid Fever by the Thiazole Derivatives of Sulfanilamide. A Preliminary Report of Four Cases, *South M J* **33** 645-648 (June) 1940.

68 Porter, J. R., and Hale, W. H. Effect of Sulfanilamide and Sulfapyridine on Experimental Infections with *Listerella* and *Erysipelothrix* in Mice, *Proc Soc Exper Biol & Med* **42** 47-50 (Oct) 1939.

69 Schwartz, W. F., and Freeman, H. E. Sulfanilamide in Treatment of Chancroid, *J A M A* **114** 946-947 (March 16) 1940.

Sulfanilamide rendered 20 per cent of 77 patients with trachoma symptom free, 40 per cent were improved, and 40 per cent were unchanged⁷⁰ Since the disease remained active, other supplementary measures seem to be needed

Contrary to earlier favorable reports, sulfanilamide had no beneficial effect on experimental gas gangrene⁷¹ An antiserum for *Clostridium welchii* was effective in treatment

Sulfapyridine protected mice against experimental infection with *Haemophilus influenzae*,⁷² and clinical trial in a few patients with this infection has also given promise of success⁷³ No benefit was observed in guinea pigs with Rocky Mountain spotted fever or with typhus,⁷⁴ or in mice infected with anthrax bacilli⁷⁵

In the accompanying table infections are grouped to show the relative effectiveness of chemotherapy for them The chart emphasizes the

Effectiveness of Chemotherapy in Diseases

Curative in	Of Doubtful Value in	Of Little or No Value in
Streptococcus haemolyticus in infections (except in tonsillitis and in presence of pus)	Brucellosis	Purulent lesions with any bacteria
Pneumococcus pneumonia, septicemia, meningitis	Staphylococcal infections	Tuberculosis
Gonococcus urethritis arthritis	Ulcerative endocarditis	Rickettsial diseases
Meningococcus meningitis	Ulcerative colitis	Almost all virus diseases
Colon bacillus infections of urinary tract	Scarlet fever	Streptococcus viridans endocarditis
	Typhoid fever	Rheumatic fever
	<i>Clostridium welchii</i> infections	Rheumatoid arthritis
	Friedlander's bacillus infections	Infectious mononucleosis
	Venereal lymphogranuloma	Malaria
	Trachoma	Fungous infections
	Plague	Spirochetal diseases
	Chancroid	Trichinosis
	Meningitis due to Pfeiffer's bacillus	Tularemia

necessity of etiologic diagnoses Rearrangement of the list may be anticipated as knowledge increases and as new and more efficient drugs are made

70 Juhanelle, L. A., Lane, J. F., and Whitted, W. P. Effect of Sulfanilamide on the Course of Trachoma, *Am J Ophth* **22** 1244-1252 (Nov.) 1939

71 Kendrick, D. B. Treatment of Gas Gangrene Infections in Guinea Pigs with Neoprontosil Sulfanilamide and Sulfapyridine. An Experimental Study, *J Clin Investigation* **18** 593-596 (Sept.) 1939

72 Pittman, M. The Protection of Mice Against *Hemophilus Influenzae* (Non-Type-Specific) with Sulfapyridine, *Pub Health Rep* **54** 1769-1775 (Sept.) 1939

73 Roche, E. H., and Caughey, J. E. Influenzal Meningitis Treated with M & B 693, *Lancet* **2** 635-638 (Sept 16) 1939 Hamilton, T. R., and Neff, F. C. Influenzal Meningitis with Bacteremia Treated with Sulfapyridine. Recovery, *J A M A* **113** 1123-1125 (Sept 16) 1939

74 Topping, N. H. Experimental Rocky Mountain Spotted Fever and Endemic Typhus Treated with Prontosil or Sulfapyridine, *Pub Health Rep* **54** 1143-1147 (June 30) 1939

75 Crunkshank, J. C. Chemotherapy of Experimental Anthrax Infection, *Lancet* **1** 681-684 (Sept 23) 1939

PNEUMONIA

The chemotherapy of pneumonia is discussed on page 480

Wood ⁷⁶ recommends the use of the skin test with specific pneumococcus polysaccharide proposed by Francis as a guide to determine whether enough antipneumococcus serum has been injected. The test, it is claimed, when positive invariably denotes that recovery has begun, when negative, it indicates the need of further serum therapy. The test, Wood believes, is not used as widely as it should be, because many who have tried it did not apply it correctly or interpret its results properly. He presents evidence that the immediate wheal and erythema of the skin reaction are due to the local union of antibody and polysaccharide in the skin, perhaps in the nature of a local precipitin reaction, and indicate the presence of type-specific antibodies in the blood. Edwards and his associates ⁷⁷ also believe the test to be valuable but not infallible.

In another paper Wood ⁷⁸ points out the great variability in the amount of antibody required in the individual case of pneumococcal pneumonia. He deplores the adoption of routine injection of large amounts (100,000 or more units) of serum as wasteful, since all patients do not need so much. This seems to be especially true since the introduction of sulfapyridine. By the use of the Francis skin test it is possible to gauge the amount of serum needed with considerable accuracy. No patient who failed to show a positive skin reaction recovered from pneumonia.

Hall ⁷⁹ brings to attention an important hazard in obstetric practice, namely, that of aspiration pneumonitis. Unfortunately, only a few of the 15 examples of the condition he presents conform to the criteria of pneumonitis. In many, from the meager data given, it is impossible to give an opinion, in others, atelectasis or embolism may have occurred. There is no doubt, however, that vomiting or the development of a shocklike syndrome during parturition as a result of natural causes or from overmedication is a serious occurrence and ought to be guarded against more carefully. In reading over his case reports one is struck

⁷⁶ Wood, W. B. The Control of the Dosage of Antiserum in the Treatment of Pneumococcal Pneumonia. I. A Study of the Mechanism of the Skin Reaction to Type Specific Polysaccharide, *J. Clin. Investigation* **19** 95-104 (Jan.) 1940.

⁷⁷ Edwards, J. C., Hoaglund, C. L., and Thompson, L. D. Type Specific Polysaccharide Skin Test in Serum Therapy of Pneumonia, *J. A. M. A.* **113** 1876-1880 (Nov. 18) 1939.

⁷⁸ Wood, W. B. The Control of the Dosage of Antiserum in the Treatment of Pneumococcal Pneumonia. II. The Clinical Application of the Francis Skin Test, *J. Clin. Investigation* **19** 105-121 (Jan.) 1940.

⁷⁹ Hall, C. C. Aspiration Pneumonitis. An Obstetric Hazard, *J. A. M. A.* **114** 728-733 (March 2) 1940.

by the number of drugs employed ante partum. In a fatal case the patient received sodium allyl, scopolamine hydrobromide, solution of posterior pituitary, morphine sulfate and gas anesthesia all within a period of four and one-half hours. It is not surprising that she vomited. Soon after delivery a shocklike condition was treated with atropine, oxygen-carbon dioxide, sucrose solution, metrazol and, later, transfusions of blood. Some of these, no doubt, are valuable remedies, but the variety used is reminiscent of the old days of polypharmacy, except that instead of being used all at once the drugs are applied in rapid succession. As a result, one may wonder, perhaps, not so much why untoward effects occur but why they do not occur oftener.

Oil Aspiration Pneumonia—Several papers have appeared on this subject. Graef⁸⁰ stressed the pathologic features. He urges that intra-nasal medication with liquid petrolatum as a lubricant be stopped, because of the difficulty in expelling oil once it gets into the lung. Bishop⁸¹ reviews 136 reported cases and gives a long list of references. To show the difficulty in arriving at a correct diagnosis of lipid pneumonia, Thomas and Rienhoff⁸² report a case in which pulmonary carcinoma was suspected. The patient was operated on and died, at necropsy aspiration of oil was found to have been the cause of the trouble. It was then learned that the patient had used an oil spray in his nose over a long period.

Chemical Pneumonia—Considerable controversy, especially in Europe, exists over the nature of the so-called Thomas slag meal pneumonia⁸³. Thomas slag is a by-product of certain methods of steel founding and is used as a fertilizer. It is a powdery substance containing, among other chemicals, phosphoric acid, calcium hydroxide, silicic acid and manganese dioxide. A high pneumonia rate has been noted among workers who handle the slag. Some believe the calcium hydroxide to be the irritant, others the manganese, but Gundel⁸⁴ minimizes the danger of these substances as a cause, since a similar incidence of pneumonia occurs among workers in other industries not associated with these

80 Graef, I. Studies in Lipid Pneumonia. I Lipid Pneumonia Due to Cod Liver Oil, II Lipid Pneumonia Due to Liquid Petrolatum, Arch Path **28** 613-667 (Nov) 1939

81 Bishop, P. G. C. Oil Aspiration Pneumonia and Pneumolipoidosis, Ann Int Med **13** 1327-1359 (Feb) 1940

82 Thomas, H. M., and Rienhoff, W. F. Lipoid Cell Pneumonia. Adult Type, South M J **32** 1077-1080 (Nov) 1939

83 Kahlstorf, A. Die Thomasschlackenmehlpneumonie, Deutsches Arch f klin Med **184** 466-483 (Aug 1) 1939

84 Gundel, M. Pneumoniehaufungen in gewerblichen Betrieben, Bericht über den VIII Internationalen Kongress für Unfallmedizin und Berufskrankheiten, Frankfurt, September 1938, Leipzig, Georg Thieme, 1939, pp 1047-1054

chemicals His view is in line with that of American investigators, who emphasize the importance of overheating and chilling as to the pneumonia in steel mills Gundel claims to have reduced the morbidity by specific vaccination with pneumococci of types I and II Vaccines, however, were unsuccessful in Norway, where manganese in the smoke is believed to be responsible⁸⁵

Two more uncontrolled and unconvincing reports⁸⁶ have appeared concerning roentgen ray therapy in pneumonia According to one author, the fact that the mortality rate (20 per cent) was the same in the patients treated with roentgen radiation as in those who had only a diagnostic roentgenogram made of the chest shows that even the roentgen rays used in making a plate of the chest (1) are beneficial in pneumonia To test whether or not roentgen rays exert any influence in pneumococcal infections under controlled conditions, Havens and Casper⁸⁷ injected pneumococci intradermally in rabbits and treated them The rays were ineffective in small doses, and when larger doses were used the mortality rate was greater in the treated than in the untreated animals

Experiments with serum therapy by Kempf and Nungester⁸⁸ did not reveal any considerable penetration of specific antiserum into the alveoli of the lungs of infected rats The blood is often rendered temporarily pneumococcus-free, but not the lungs Perhaps some other mechanism, in addition, plays a role in recovery from pneumococcal infection Further studies by Robertson and Van Sant⁸⁹ indicate that macrophages are more able to engulf and digest pneumococci than polymorphonuclear leukocytes and that macrophages from immunized animals are no more active than those from normal ones, both depend chiefly on opsonins for their activity

Rich and McKee⁹⁰ also point to the leukocytes as factors of great importance in controlling infection These observers show that rabbits

85 Manganese in Factory Smoke and Pneumonia in Sauda (Norway), *Foreign Letters, J A M A* **113** 1426 (Oct 7) 1939

86 Scott, W R X-Ray Therapy in the Treatment of Acute Pneumonia, *Radiology* **33** 331-349 (Sept) 1939 Solis-Cohen, L, and Levine, S Roentgen Treatment of Lobar Pneumonia, *Am J Roentgenol* **42** 411-417 (Sept) 1939

87 Havens, W P, and Casper, S Roentgen Ray Therapy in Pneumococcus Type I Infection in Rabbits, *Proc Soc Exper Biol & Med* **42** 179-180 (Oct) 1939

88 Kempf, A H, and Nungester, W J Action of Antipneumococcus Serum in the Pneumonic Rat and Its Penetration into the Pulmonary Lesion, *J Infect Dis* **65** 1-11 (July-Aug) 1939

89 Robertson, O H, and Van Sant, H A Comparative Study of Phagocytes and Digestion of Pneumococci by Macrophages and Polymorphonuclear Leucocytes in Normal and Immune Dogs, *J Immunol* **37** 571-597 (Dec) 1939

90 Rich, A R, and McKee, C M The Pathogenicity of Avirulent Pneumococci for Animals Deprived of Leucocytes, *Bull Johns Hopkins Hosp* **64** 434-446 1939

deprived of their circulating leukocytes by the injection of benzene can be infected by "R" pneumococci, which are avirulent and promptly destroyed in normal animals. They believe that the ability of "R" pneumococci to become actively invasive and destructive is due chiefly, if not entirely, to the absence of circulating phagocytic cells. In this work and in that previously reported they seem to overlook the fact that in a rabbit severely poisoned with benzene many other changes take place besides a simple removal of leukocytes which may render animals susceptible to bacteria ordinarily avirulent in normal ones. They themselves question whether several animals did not die from benzene poisoning and not from the infection.

It seems to me that in many ideas concerning the prevention of and recovery from infections far too much importance has been attributed to the leukocytes. So much attention has been given to them, perhaps, because they can be easily studied both by enumeration and by histologic technics. They no doubt are important in the process, but many other factors are operative too.

STREPTOCOCCI

Boisvert⁹¹ tested the reliability of the antifibrinolysin test for the diagnosis of recent infection with the hemolytic streptococcus. The test was at first believed to be specific, but it has been found to be positive in infections caused by other bacteria. In Boisvert's experience the test was strongly positive in many cases of pneumococcic pneumonia, but further study revealed that although the test was positive during the disease the positive reaction tended to diminish rapidly afterward, in contrast to the reactions in other infections, in which several reaction types or "trends" were noted during the disease. In some the test was never positive, in some it was persistent, in a few it was intermittently positive and in others it was negative during the acute stage and positive later. The last trend was observed in most cases of infection with the hemolytic streptococcus, and in rheumatic fever the test was usually continuously high.

Antistreptolysin was present in 80 per cent of patients with scarlet fever and in the majority of patients with acute rheumatic fever and chorea.⁹² It was absent as a rule in patients with rheumatoid arthritis despite the frequent presence of agglutinins for the same strain of streptococci used as antigen for the antistreptolysin test. The test was helpful in the diagnosis of atypical rheumatic fever, since it is seldom

⁹¹ Boisvert, P. L. The Streptococcal Antifibrinolysin Test in Clinical Use, *J Clin Investigation* **19** 65-74 (Jan) 1940

⁹² Bunim, J. J. and McEwen, C. The Antistreptolysin Test in Rheumatic Fever, Arthritis and Other Diseases. *J Clin Investigation* **19** 75-82 (Jan) 1940

positive in other forms of joint disease. Its presence in any disease does not necessarily prove that the hemolytic streptococcus is the cause. Some go so far as to say that the presence of agglutinins for streptococci in rheumatic fever does not any more indicate a causal relationship than the presence of agglutinins in rickettsial diseases (Weil-Felix reaction) indicates a causal relationship of *Bacillus proteus* to these diseases.

The first practical application of a preparation called gramicidin in the treatment of mastitis caused by *Streptococcus agalactiae contagiosae* in cows met with considerable success.^{92a} Gramicidin is the alcohol-soluble, water-insoluble substance isolated by Dubos from cultures of a sporulating bacillus. It is bactericidal for numerous gram-positive bacteria.

INFLUENZA

Nelson and Oliphant⁹³ studied the pathologic aspects of infection caused by the virus of epidemic influenza in mice. In addition to the typical histologic changes in the mucous membranes of the respiratory tract and lungs as previously described by others, slight lesions were present in the liver, spleen, thymus and kidney, but none in the adrenal glands, brain, thyroid gland, heart, pancreas or gastrointestinal tract. In ferrets^{93a} lesions were found only in the nose and lungs.

Straub⁹⁴ reports studies similar to those of Francis and Stuart-Harris in 1938 on the effects of the virus of epidemic influenza on the mucous membranes of the respiratory tract in rats. The virus specifically affects the epithelium from the bronchioles to the bifurcation of the trachea. It causes catarrhal bronchitis with collapse of lung tissue. The collapse itself is nonspecific and is merely a complication of the obstruction. Severe infection leaves metaplastic epithelial changes, which render mice temporarily immune to reinfection. Mild attacks which leave no changes in the mucous membranes give no immunity.

Another factor in immunity against the virus of epidemic influenza may reside in certain properties of the nasal secretion. Burnet and his

92a Little, R. B., Dubos, R. J., and Hotchkiss, R. D. Action of Gramicidin on Streptococci of Bovine Mastitis, *Proc. Soc. Exper. Biol. & Med.* **44**: 444-445 (June) 1940.

93 Nelson, A. A., and Oliphant, J. W. Histopathological Changes in Mice Inoculated with Influenza Virus, *Pub. Health Rep.* **54**: 2044-2054 (Nov. 17) 1939.

93a Perrin, T. L., and Oliphant, J. W. Pathologic Histology of Experimental Virus Influenza in Ferrets, *Pub. Health Rep.* **55**: 1077-1086 (June 14) 1940.

94 Straub, M. The Histology of Catarrhal Influenzal Bronchitis and Collapse of the Lung in Mice Infected with Influenza Virus, *J. Path. & Bact.* **50**: 31-36 (Jan.) 1940.

associates⁹⁵ report studies on a virus-inactivating agent in the nasal secretions of certain persons who could not be deliberately infected with the virus. In the test tube such nasal secretion acts more slowly on the virus than specific antibodies do and not at all in the cold. The nature of the inactivating agent is unknown. A similar agent was studied by Francis⁹⁶

The experience of Taylor and Dreguss⁹⁷ in Hungary failed to show the effectiveness of formaldehyde-inactivated influenza virus. Little difference was noted during an epidemic between those who were vaccinated and those who were not. However, since five different strains of virus were isolated, it is possible that vaccine prepared against one strain has no effect against another. The five strains isolated tended to form a group separate from WS, PR8 and swine influenza virus⁹⁸. A new approach to the problem of vaccine for multiple strains of influenza virus is suggested by the observations of Horsfall and Lennette⁹⁹. They made a vaccine from ferrets which had had both influenza and a subsequent incidental distemper-like disease. The vaccine, freshly prepared, served as a surprisingly efficient immunizing agent against several different strains of influenza virus and against the virus of dog distemper. Vaccines prepared from animals infected with either influenza virus or distemper virus alone were unsatisfactory, and, disappointingly, repeated attempts to make vaccines from animals which had had both influenza and distemper were seldom as successful as the vaccine of the original experiment.

During the outbreak in England in 1939 further attempts were made to test the value of anti-influenza vaccine¹⁰⁰. The results were disappointing and inconclusive. Unfortunately, in spite of several pessimistic reports, commercial exploitation of "influenza virus vaccine" has already begun in England, where the sale of such uncertain

95 Burnet, F. M., Lush, D., and Jackson, A. V. A Virus-Inactivating Agent from Human Nasal Secretion, *Brit. J. Exper. Path.* **20** 377-385 (Oct.) 1939.

96 Francis, T. The Inactivation of Epidemic Influenza Virus by Nasal Secretions of Human Individuals, *Science* **91** 198-199 (Feb. 23) 1940.

97 Taylor, R. M., and Dreguss, M. An Experiment in Immunization Against Influenza with a Formaldehyde-Inactivated Virus, *Am. J. Hyg. (Sect. B)* **31** 31-35 (Jan.) 1940.

98 Taylor, R. M., Dreguss, M., and DeRitis, F. Antigenic Behavior of Certain Hungarian Strains of Epidemic Influenza Virus, *Am. J. Hyg. (Sect. B)* **31** 36-45 (Jan.) 1940.

99 Horsfall, F. L., and Lennette, E. H. A Complex Vaccine Effective Against Different Strains of Influenza Virus, *Science* **91** 492-494 (May 24) 1940.

100 Stuart-Harris, C. H., Smith, W., and Andrewes, C. H. The Influenza Epidemic of January-March 1939, *Lancet* **1** 205-211 (Feb. 3) 1940.

products is under less control than in the United States (see advertisement in *Lancet*, Feb 3, 1940)

Taylor¹⁰¹ was able to transfer infections from human patients directly to hamsters. Infections in these mouselike animals were proved by the development of specific antibodies against known strains of influenza.

Chapman and Hyde¹⁰² isolated the virus of influenza from 6 of 9 patients in 1936-1937. They cultured the virus on the chorioallantoic membrane of the chick embryo and found this medium to be as sensitive as the ferret for primary isolation of the virus. They were not successful in isolating a virus from patients with the common cold.

Prevalent Influenza-like Disease—Stokes, Havens and I¹⁶ report studies on a widespread influenza-like epidemic infection of the respiratory tract in the winter of 1939. Fifty per cent of a group of 800 persons were ill, most of them (87 per cent) with a mild form of the disease, but 6 per cent were confined to bed with nasopharyngolaryngotracheobronchitis, and another 6 per cent had pneumonia in addition. Maxfield¹⁰³ experienced a similar outbreak in Texas and Murray¹⁰⁴ one in Massachusetts. Other observers also studied coincident epidemics and focused their attention chiefly on the severely sick patients, calling the disease various forms of pneumonia. This we believe to be misleading, since in our experience the patients with severe disease comprised only a small proportion (6 per cent) of all those involved by an otherwise mild infection. We suggest that until further studies reveal the etiologic agent, the entity be called "grip," in contrast to epidemic influenza, which is associated with a known filtrable virus. No success attended our efforts to isolate the causative agent in 1939.

Similar results are published by two British groups. Scattered epidemics in England, simultaneous with ours in the winter of 1939, were studied and compared with earlier epidemics of a clinically similar disease in which the virus of influenza seemed to be operative. For the most part, a clinical differentiation could not be made between cases in which the virus of influenza was involved and those in which it could not be detected. The authors¹⁰⁰ decided that each outbreak

101 Taylor, R. M. Detection of Human Influenza Virus in Throat Washings by Immunity Response in Syrian Hamster (*Cricetus Auratus*), *Proc Soc Exper Biol & Med* **43** 541-542 (March) 1940.

102 Chapman, J., and Hyde, R. R. Antigenic Differences in Viruses from Cases of Influenza and Colds, *Am J Hyg (Sect B)* **31** 46-67 (Jan) 1940.

103 Maxfield, J. R., Jr. Atypical Pneumonia with Leucopenia, *Texas State J Med* **35** 340-345 (Sept) 1939.

104 Murray, M. E., Jr. Atypical Bronchopneumonia of Unknown Etiology, Possibly Due to a Filterable Virus, *New England J Med* **222** 565-573 (April) 1940.

consisted of a proportion of cases of infection with the virus of epidemic influenza mixed with many other cases of some clinically similar but etiologically different disease. Martin and Fairbrother's experience¹⁰⁵ indicated, as ours did in 1938, that an unknown virus may be the cause. They also isolated an elusive filtrable agent but were unable to prove its etiologic relation to the disease.

Except for a few differences, the clinical description of their cases closely matches ours. Sweating, an outstanding feature in our cases is, however, scarcely mentioned by the British group. This and certain other minor clinical differences may be actual, but since our patients were continuously under our observation during their illness, we feel that our observations were perhaps more detailed and more carefully recorded than those made by numerous persons in scattered epidemics.

Simultaneous with these epidemics of a disease of the respiratory tract of unknown origin, Horsfall and his collaborators¹⁰⁶ report 4 localized outbreaks of true epidemic influenza in New York, from which influenza virus was recovered. The height of the epidemics in mid-February coincided exactly with the one we report. Obviously, and as would be expected, two or more infections by different etiologic agents may occur in different places or in the same place at the same time. The clinical aspects of the two diseases are so similar in most cases that differentiation without special study is impossible. Similar to the previous experience of others, the New York investigators detected neutralizing antibodies against the virus of influenza in persons who had been in contact with patients with influenza but who had not been sick, suggesting that subclinical, symptomless infection had occurred in these persons.

Jennison and Edgerton¹⁰⁷ made interesting observations, using high speed photography on the expulsion of droplets of secretion during sneezing. They had in mind a study of droplet infection, which apparently plays so great a role in acute diseases of the respiratory tract. The droplets, they found, were so small and had so great a velocity as to cause rapid evaporation. The dry bacteria or viruses, if present, could then float about in the air as potential invaders of susceptible hosts.

¹⁰⁵ Martin A. E., and Fairbrother, R. W. An Epidemic of Apparent Influenza, *Lancet* **2** 1313-1315 (Dec. 23) 1939.

¹⁰⁶ Horsfall, F. L., Hahn, R. G., and Rickard, E. R. Four Recent Influenza Epidemics. An Experimental Study, *J. Clin. Investigation* **19** 379-392 (March) 1940.

¹⁰⁷ Jennison, M. W., and Edgerton, H. E. Droplet Infection of Air. High Speed Photography of Droplet Production by Sneezing, *Proc. Soc. Exper. Biol. & Med.* **43** 455-458 (March) 1940.

RHEUMATIC FEVER

The observations of Stroud and Twaddle¹⁰⁸ lend more support to the plan for providing specialized institutional care for children with rheumatic heart disease. A number of such sanatoriums are scattered throughout the country, and it seems desirable to establish more of them to assist children to adjust themselves physically and emotionally to their handicap. The course of nearly 700 afflicted children was followed for fifteen years. Twenty-one per cent died. The greatest mortality occurred from three to five years after the first attack of rheumatic fever. Forty-eight per cent of the deaths occurred in the first six years. Of 27 girls who later became pregnant, congestive heart failure developed in only 1.

The characteristic signs of permanent valvular defects in one series¹⁰⁹ of 314 patients, if not present at the time of the original illness, appeared during the first decade in 25 per cent. The delayed appearance was usually associated with evidence of recurrence of rheumatic fever.

Jones¹¹⁰ critically reviews the theories as to the cause of rheumatic fever in an impartial manner and concludes that the cause is as yet unknown. He refers to his interesting studies with Mote, presented at the Microbiologic Congress in New York in September 1939. A filtrable virus, not unlike that of influenza, was recovered from patients with rheumatic fever. It was apparently not found in normal persons, but the possibility that it may have been accidentally encountered in mice was not excluded. They do not suggest any etiologic relationship of the virus to the rheumatic fever.

Collis¹¹¹ in his review of bacteriologic studies of rheumatic fever still places much emphasis on the hemolytic streptococcus as a possible cause.

RHEUMATOID ARTHRITIS

Cobb, Bauer and Whiting¹¹² briefly review the difficulties involved in discovering the cause of rheumatoid arthritis. While evidence points to an underlying infection in most cases, many observers before the advent of bacteriology favored the neurogenic theory because of the

108 Stroud, W. D., and Twaddle, P. H. Fifteen Years Observation of Children with Rheumatic Heart Disease, *J. A. M. A.* **114** 629-634 (Feb. 24) 1940.

109 Bland, E. F., and Jones, T. D. The Delayed Appearance of Heart Disease After Rheumatic Fever, *J. A. M. A.* **113** 1380-1383 (Oct. 7) 1940.

110 Jones, T. D. The Etiology of Rheumatic Fever. A Discussion, *J. Pediat.* **15** 772-785 (Dec.) 1939.

111 Collis, W. R. F. Bacteriology of Rheumatic Fever, *Lancet* **2** 817-820 (Oct. 14) 1939.

112 Cobb, S., Bauer, W., and Whiting, I. Environmental Factors in Rheumatoid Arthritis, *J. A. M. A.* **113** 608-670 (Aug. 19) 1939.

frequent symmetrical distribution of the diseased joints. The authors bring forth more evidence to emphasize the importance of environmental stress, poverty, grief and family worries, which in certain instances seemed to be the only important inciting factors in the onset or exacerbations of rheumatoid arthritis. They recommend a more careful and detailed inquiry into the social and psychiatric events in all patients with the disease.

In another timely paper Margolis and Eisenstein¹¹³ point out the uselessness of all supposedly specific therapeutic measures used in treating chronic arthritis. Sulfur, vaccines, fever therapy and sulfanilamide have all been disappointing. Gold salts show but little promise and may cause harmful side effects. The patients of Sidel and Abrams¹¹⁴ responded just as satisfactorily to the subcutaneous injection of salt solution as to the intravenous injection of polyvalent streptococcus vaccine. The psychologic effect, they believe, seems more important than the substance injected. I may add that the percentage of patients improved in their report—72 and 68 per cent, respectively—is similar to what may be expected in the natural course of the disease without any treatment.

For a comprehensive review of the subject of rheumatic disease and its ramifications, the reader is referred to the sixth annual review of a special committee organized for this purpose¹¹⁵. Over a thousand titles are listed in the bibliography.

FOCAL INFECTION

Havens and I¹¹⁶ gathered much of the pertinent material which has accumulated since Holman's paper in 1928 to support the case against the removal of teeth and tonsils in the hope of preventing or favorably influencing systemic disease. We show that the results of the practice over a period of twenty-five years do not justify it and conclude that (a) the theory of focal infection in the sense of the term used is unproved, (b) the infectious agents are unknown, (c) large groups of

113 Margolis, H. M., and Eisenstein, V. W. Some Specific Measures in the Treatment of Rheumatoid Arthritis, *J. A. M. A.* **114** 1429-1434 (April 13) 1940.

114 Sidel, N., and Abrams, M. I. Treatment of Chronic Arthritis. Results of Vaccine Therapy with Saline Injections Used as Controls, *J. A. M. A.* **114** 1740-1742 (May 4) 1940.

115 Hench, P. S., Bauer, W., Dawson, M. H., Hall, F., Holbrook, W. P.; Kev, I. A., and McEwen, C. The Problem of Rheumatism and Arthritis. Review of American and English Literature for 1938 (Sixth Rheumatism Review), Part I, *Ann. Int. Med.* **13** 1655-1739 (March) 1940, Part II, *ibid.* **13** 1837-1990 (April) 1940.

116 Reimann, H. A., and Havens, W. P. Focal Infection and Systemic Disease. A Critical Appraisal, the Case Against Indiscriminate Removal of Teeth and Tonsils, *J. A. M. A.* **114** 1-6 (Jan. 6) 1940.

persons whose tonsils are present are no worse than those whose tonsils are out, (d) patients whose teeth and tonsils are removed usually continue to suffer from the ailment for which they were removed, (e) beneficial effects when they do occur can seldom be ascribed to surgical procedures alone, (f) beneficial effects which occasionally occur after surgical measures are often outweighed by harmful effects or by absence of any effect at all, and (g) many suggestive foci of infection heal after recovery from systemic disease, or when the general health is improved with hygienic and dietary measures. If an abscess or a chronic infection around a tooth is present with reasonable certainty or if the tonsils are actually infected and the infection gives rise to repeated attacks of sickness, surgical measures may be indicated in selected patients.

Since our review of the subject, other papers supporting our views have appeared. Brown found that 62.8 per cent of the psychiatric patients had what are usually called foci of infection, and yet were without the diseases usually associated with them.^{116a} Grossman¹¹⁷ concludes from the evidence he presents that the indiscriminate extraction of pulpless teeth is unwarranted. In one study⁴⁴ children with and without tonsils were equally susceptible to infection with hemolytic streptococci, but infection, once established, persisted longer in children with tonsils. Illingworth¹¹⁸ concludes that tonsillectomy in childhood does not prevent or limit nephritis, the procedure may even predispose patients to nephritis or actually cause it. We feel, however, that he exaggerates the danger. Another case in which endocarditis followed extraction of teeth was reported,¹¹⁹ and others¹²⁰ point out the needlessness of removing tonsils for certain allergic conditions in children. The authors refer to the report that 1,235,000 tonsillectomies are performed each year in the United States. It would seem that many of these operations were needlessly done, and a time has come to check this "slaughter of tonsils," as it has been called.

It is also surprising to learn that a certain authority¹²¹ infers not only that extraction of teeth and tonsillectomy may be helpful in the treatment of diabetes but also that these procedures may prevent the

116a Brown, C. H. Foci of Infection in Psychiatric Patients, *Am J M Sc* **199** 539-545 (April) 1940

117 Grossman, L. I. Present Status of the Pulpless Tooth, *Ann Int Med* **13** 1805-1813 (April) 1940

118 Illingworth, R. S. Tonsillectomy and Nephritis of Childhood, *Lancet* **2** 1013-1016 (Nov 11) 1939

119 Palmer, H. D., and Kempf, M. Streptococcus Viridans Bacteremia Following Extraction of Teeth, *J A M A* **113** 1788-1792 (Nov 11) 1939

120 Hansel, F. K., and Chang, C. S. Relation of Allergy and Tonsillectomy in Children, *Arch Otolaryng* **31** 45 (Jan) 1940

121 Wilder, R. M. Diseases of Metabolism, in Barr, D. P. *Modern Therapy in General Practice*, Baltimore, Williams & Wilkins Company, 1940, p. 888

development of diabetes in blood relatives of the patient¹ Sepsis, if proved, no doubt, may provoke the development of diabetes or intensify it, but we believe the statement that "the teeth and tonsils more frequently than other sites are likely to harbor infection" cannot be supported with proof One may speculate, first, on the presence of "infection" in other parts of the body less accessible to examination and, second, whether or not suspected infection may not heal spontaneously once the diabetes is controlled The uncritical attitude with which many of the operations for the removal of foci of infection are performed reflects no credit on many specialists in laryngology Since publishing our critique we have received letters from two friends of the late Dr Frank Billings who, they said, regretted ever having raised the question of focal infection after he saw the extremes to which the theory was carried

As examples of the type of misleading and uncontrolled information which editors of medical journals occasionally accept are papers in which authors¹²² recommend the extraction of teeth to prevent pulmonary hemorrhage in patients with tuberculosis and tonsillectomy for the treatment of granulocytopenia

Chronic Appendicitis—In a manner somewhat different from that of our attack on the question of focal infection, Alvarez¹²³ has inquired into the rationale of performing appendectomy for "chronic appendicitis" He was astonished to find that among a group of 255 patients who were operated on for this reason, only 25 had had pain and soreness in the right lower quadrant of the abdomen with indigestion Many were obviously neurotic persons Furthermore, only 2 of the group were cured In contrast to this, of course, there were 130 patients who had had at least one or more previous attacks of what might have been appendicitis Of these, 87 (67 per cent) were cured by appendectomy Alvarez points out that a person who has never had an acute attack of appendicitis who submits to appendectomy has 1 chance in 100 of relief from his complaints, he has also the same chance of dying from the operation True chronic appendicitis, he believes, is one of the rarest of intra-abdominal diseases

It seems to me that if the number of unnecessary appendectomies and tonsillectomies were reduced, it would diminish to a large extent the cost of medical care, about which we read and hear so much

¹²² Sprague, C H Hemorrhage in Pulmonary Tuberculosis Dental Focal Infection as a Principal Cause, *Northwest Med* **38** 475 (Dec) 1939 Holsti, O, Meurman Y and Virkkunen M Tonsillectomy in Emergency Treatment of Angina Granulocytopenia States, *Acta med Scandinav* **103** 430 (March 8) 1940

¹²³ Alvarez, W C Chronic Appendicitis, *I A M A* **114** 1301-1306 (April 6) 1940

BACILLARY DISEASES

There was an outbreak of a severe form of dysentery caused by *Shigella dysenteriae* in Michigan¹²⁴ Ten deaths occurred among 45 patients The average age of the patients was 8, and the majority were among the poor An epidemic of dysentery in a Connecticut hospital resulted from the use of ice contaminated by a carrier¹²⁵

Felsen¹²⁶ reports success in treating patients with severe dysentery by giving them blood from donors who had previously been vaccinated with dysentery bacilli, colon bacilli and enterococci

Undulant Fever —Parsons, Poston and Wise¹²⁷ isolated *Brucella melitensis* from the lymph nodes of 7 patients with Hodgkin's disease and from none of the lymph nodes of 50 controls The serum from patients with Hodgkin's disease, however, failed to agglutinate brucellas In another paper,¹²⁸ describing wider experience, it is stated that *Brucella* was cultivated from the lymph nodes of 10 of 19 patients with Hodgkin's disease but from only 1 of 67 controls The inference from this work may be that *Brucella* is etiologically related to Hodgkin's disease The authors claim to be unable to differentiate chronic brucellosis of the glandular type from Hodgkin's disease It must be said, however, that it is unsafe to emphasize histopathologic changes as indicating etiologic relationships Furthermore, there are many who still remember the controversies regarding the relationship of the tubercle bacillus and a diphtheroid bacillus to Hodgkin's disease Much more work will have to be done before *Brucella* is suspected seriously as the etiologic agent Information, as yet unpublished, from at least two other laboratories indicates that it was not possible to confirm the results of Parson and Poston

Robinson and Evans¹²⁹ made a clinical survey in a county of North Carolina of 325 cases in which patients suffered from chronic ill health, usually with low grade fever, psychoneurosis and unexplained abortions In 22 of these cases the illness was diagnosed as chronic brucellosis The authors show that in diagnosis too much reliance is often placed on the

124 Block, N B, and Ferguson, W An Outbreak of Shiga Dysentery in Michigan, 1938, *Am J Pub Health* **30** 43-52 (Jan) 1940

125 Godfrey, E J, and Pond, M A A Hospital Epidemic of Flexner Dysentery Caused by Contaminated Ice, *J A M A* **114** 1151-1154 (March 30) 1940

126 Felsen, J Clinical Notes on the Use of Immunized Donors in Chronic Bacillary Dysentery, *Am J Digest Dis* **7** 81-89 (Feb) 1940

127 Parsons, P B Poston, M A, and Wise, B The Pathology of Human Brucellosis, *Am J Path* **15** 634-635 (Sept) 1939

128 Poston, M A, and Parsons, P B Isolation of *Brucella* from Lymph Nodes, *J Infect Dis* **66** 86-90 (Jan-Feb) 1940

129 Robinson, F H, and Evans, A C Chronic Brucellosis in Charlotte, North Carolina, *J A M A* **113** 201-207 (July 15) 1939

agglutination test, the skin test or the opsonocytophagic test, the last being the least trustworthy. The best test, of course, is the isolation of the causative organism, this was isolated in 5 instances. The authors outline the clinical characteristics of the chronic form of the disease but overemphasize, it seems to me, the difficulties in diagnosis. In my experience undulant fever in its more acute form is not difficult to recognize. Like other infections, such as typhoid fever and tuberculosis, certain low grade or chronic forms may be confusing, but once the condition is in mind, appropriate observations and tests usually solve the problem.

A report of the water-borne outbreak among students in a bacteriologic laboratory was made¹³⁰. Thirty-one per cent of 210 exposed students contracted the disease. Frank illness developed in 37 students and the latent form in 28. Fifteen other persons who had been in the building were infected. It was found that faulty plumbing by which sewage entered the water supply was the probable cause of the epidemic. The nature of the accident recalls the experience in Chicago with amebic dysentery several years ago.

Attempts are constantly under way to make an effective antiserum for brucellosis¹³¹. The results at present are unimpressive.

Tetanus—Although 9 specific serologic types of *Clostridium tetani* are known, MacLennan¹³² adds another and believes that many more exist. Nontoxigenic strains, he says, are comparatively common. In Gold's¹³³ experience with immunization against tetanus, two injections of alum-precipitated toxin produced a higher titer of antitoxin than three injections of plain toxoid. After the first injection the titer diminishes rapidly, necessitating reinjection. One week later the antitoxin titer may be from two to fifty times higher than that following the injection of 1,500 units of tetanus antitoxin. In some immunized persons the titer sixteen months later was well above the minimal protective level.

Tularemia—Since Foshay's review¹³⁴ of tularemia appeared, it has been learned that infection occurs naturally in the beaver¹³⁵ and the

130 Newitt, A. W., Koppa, T. M., and Gudakunst, D. W. Water-Borne Outbreak of *Brucella Melitensis* Infection, *Am J Pub Health* **29** 739-743 (July) 1939.

131 Huddleson, I. F., and Pennell, R. B. The Preparation and Purification of *Brucella* Antiserum, *Science* **90** 572-573 (Dec. 15) 1939.

132 MacLennan, J. D. The Serological Identification of *Cl. Tetani*, *Brit J Exper Path* **20** 371-376 (Oct.) 1939.

133 Gold, H. Active Immunization Against Tetanus, *Ann Int Med* **13** 768-782 (Nov.) 1939.

134 Foshay, L. Tularemia. A Summary of Certain Aspects of the Disease Including Methods for Early Diagnosis and the Results of Serum Treatment in Six Hundred Cases, *Medicine* **19** 1-83 (Feb.) 1940.

135 Scott, J. W. Natural Occurrence of Tularemia in Beaver and Its Transmission to Man, *Science* **91** 263-264 (March 15) 1940.

bacillus has been found in the water of three streams in Montana by members of the United States Public Health Service ¹³⁶

In spite of the favorable results reported by Foshay after the treatment of tularemia with specific immune serum, it is disappointing to read in an authoritative article ^{136a} that "there is no specific preventive or curative treatment for the disease"

Plague —Eskey and Haas, and Hampton ¹³⁷ again infer that plague infection among wild rodents is spreading eastward from the Pacific states. I have always doubted that this was the case. Since plague was first discovered in San Francisco in 1900, the disease, or one similar to it, has been found among rodents in many western states. This does not necessarily prove that the disease originated from the human patients or that it is spreading but may indicate that if one looks carefully enough one will find it in likely places. There is evidence that plague among wild rodents (sylvatic plague) is somewhat different from the classic bubonic plague carried by rats, but whether the sylvatic form has been modified from the human strain by passage through wild rodents, or whether it is a genuinely different variety, probably endemic on this continent, is impossible to state at present.

DISEASES CAUSED BY FILTRABLE VIRUSES

The latest advances in the knowledge of virus diseases were discussed at two important meetings during the past year. One was a symposium at Harvard Medical School in June 1939 and the other the Third International Congress for Microbiology at New York last September. The papers presented at both meetings are printed in book form ¹³⁸ and should be available to those interested in the subject.

The invention of a new type of electronic microscope, differing in principle from any of those now in use and capable of magnifying particles from 25,000 to 30,000 times, was announced at the RCA Electronic Research Laboratories ^{138a}. A magnification of 5,000 was the high-

136 Tularemia Infection Found in Streams, Pub Health Rep **55** 227 (Feb 9) 1940

136a Sources Symptoms and Prevention of Tularemia, Pub Health Rep **55** 667-670 (April 19) 1940

137 Eskey, C R, and Haas, V H. Plague in the Western Part of the United States, Pub Health Rep **54** 1467-1481 (Aug 11) 1939. Hampton, B C. Plague in the United States, *ibid* **55** 1143-1158 (June 28) 1940

138 Harvard School of Public Health, Symposium Virus and Rickettsial Diseases with Especial Consideration of Their Public Health Significance, Cambridge, Mass., Harvard University Press, 1940. Report of the Proceedings of the Third International Congress for Microbiology, New York, Sept 2-9, 1939, New York, The Congress, 1940

138a Zworykin Y K. An Electron Microscope for the Research Laboratory, Science **92** 51-53 (July 19) 1940

est heretofore possible with the ultraviolet ray optical microscope. It is possible that the new instrument will be helpful in further researches on the filtrable viruses and other infectious agents.

Encephalitis—Equine encephalitis, according to Jakmauh and Feemster,¹³⁹ except for a higher mortality rate, is clinically so similar to other forms of acute infectious encephalitis that without special methods an etiologic diagnosis cannot be made. An accurate diagnosis should, of course, be made in every case, and for this purpose 10 cc of blood should be withdrawn from the patient as soon as encephalitis is suspected and should be sent to a laboratory equipped to detect specific neutralizing antibodies. The virus is not present in the spinal fluid after the onset of symptoms, but is present in the brain, so that in fatal cases brain tissue may be removed at necropsy, placed in 50 per cent solution of glycerin and sent to a laboratory, where the virus may be isolated from animals inoculated with the material.

Investigators in North Dakota¹⁴⁰ observed the necessary precautions in establishing a correct diagnosis and reported an epidemic of 23 cases of equine encephalitis, which resembled the St. Louis type of encephalitis clinically yet differed in certain pathologic respects. Serum from only 1 of the 6 patients who recovered contained antibodies for the St. Louis type of virus, and serum from 4 patients neutralized the virus of western equine encephalitis. Similar diagnostic difficulties arose in California, where Howitt¹⁴¹ made her studies. Forty deaths were recorded from encephalitis in the summer of 1937. In 1938 more cases developed. The virus of western equine encephalitis was isolated from 2 patients, but the serum of nearly one half of 103 patients tested contained neutralizing antibodies for the St. Louis type of virus. It appears that both kinds of encephalitis were present. They were frequently mistaken for poliomyelitis. It seemed that equine encephalitis affected a younger age group and probably originated locally, the St. Louis type affected older patients and was probably imported by migrant laborers.

A detailed clinical and pathologic report¹⁴² of 8 cases in Boston in 1938 has been published. Here too the disease resembled the St. Louis

139 Jakmauh, P. H., and Feemster, R. T. Laboratory Diagnosis of Encephalitis Due to the Equine Virus, *New England J. Med.* **221** 653-655 (Oct. 26) 1939.

140 Breslich, P. I., Rowe, P. H., and Lehman, W. L. Epidemic Encephalitis in North Dakota, *J. A. M. A.* **113** 1722-1724 (Nov. 4) 1939.

141 Howitt, B. F. Viruses of Equine and of St. Louis Encephalitis in Relationship to Human Infections in California, 1937-1938, *Am. J. Pub. Health* **29** 1083-1097 (Oct.) 1939.

142 Farber, S., Hill, A., Connerly, M. L., and Dingle, J. H. Encephalitis in Infants and Children Caused by the Virus of the Eastern Variety of Equine Encephalitis, *J. A. M. A.* **114** 1725-1731 (May 4) 1940.

type of encephalitis in many respects. Serious neurologic disorders remained in 3 patients who survived.

An epidemic likely to have been one of equine encephalitis occurred in Iowa,¹⁴³ but since no specific tests were made, the diagnosis cannot be accepted. The presumptive clinical diagnoses were based on the clinical characteristics of the disease and on exposure to the disease in horses.

A laboratory employee who was working with the virus in a large, well equipped commercial laboratory contracted equine encephalitis and died.¹⁴⁴ The mode of infection is unknown. A vaccine like the one prepared by Beard and Finkelstein¹⁴⁵ may prevent such accidents. The latter vaccine, made from formaldehydized chick embryos and injected in doses of 1 cc, gave a satisfactory antibody response within a week. The constitutional reactions were often unpleasant. Vaccination is recommended for persons who are frequently exposed to the infection.

Lymphocytic Choriomeningitis—Experiences in England further illustrate diagnostic difficulties in recognizing the various kinds of encephalitis. MacCallum and Findlay¹⁴⁶ isolated the virus of lymphocytic choriomeningitis from the cerebrospinal fluid and the nasopharyngeal washings of several patients suspected of having acute anterior poliomyelitis. There was no evidence of the presence of the virus of poliomyelitis. Moreover, these authors, together with Scott,¹⁴⁷ also isolated two strains of virus from human beings with a disease resembling lymphocytic choriomeningitis, but the strains were different from any other known viruses. The clinical picture was similar to that of the usual form of the disease, but no cross immunity was evident from tests in animals. In "size" also, as measured by filtration through membranes, the virus differed from typical strains.

In other experimental studies on guinea pigs the virus of lymphocytic choriomeningitis seemed to be able to penetrate the unbroken skin and cause infection.¹⁴⁸ This fact may be of important epidemiologic

143 Larimer, R. N., and Wiesser, E. G. Human Equine Encephalitis, *J. Iowa M. Soc.* **29** 287-288 (July) 1939.

144 Fothergill, L. D., Holden, M., and Wyckoff, R. W. G. Western Equine Encephalomyelitis in a Laboratory Worker, *J. A. M. A.* **113** 206-207 (July 15) 1939.

145 Beard, J. W., and Finkelstein, H. Vaccination of Man Against Virus of Equine Encephalomyelitis (Eastern and Western Strains) *J. Immunol.* **38** 117-136 (Feb.) 1940.

146 MacCallum, F. O., and Findlay, G. M. Lymphocytic Choriomeningitis: Isolation of the Virus from the Nasopharynx, *Lancet* **1** 1370-1373 (June 17) 1939.

147 MacCallum, F. O., Findlay, G. M., and Scott, T. M. Pseudo-Lymphocytic Choriomeningitis, *Brit. J. Exper. Path.* **20** 260-269 (June) 1939.

148 Shaughnessy, H. J., and Zichis, J. Infection of Guinea Pigs by Application of Virus of Lymphocytic Choriomeningitis to Their Normal Skins, *Proc. Soc. Exper. Biol. & Med.* **42** 755-757 (Dec.) 1939.

significance More evidence is presented that house mice serve as a reservoir for the infection ^{148a}

Herpes Simplex—Anderson ¹⁴⁹ published further evidence of the modification of the tropism of a filtrable virus by artificial means A neurotropic strain of the virus of herpes simplex was changed by growth in chick embryos so that it no longer caused keratitis and encephalitis in rabbits but attacked the viscera instead She has not yet determined whether the induced change of tropism or "mutation" is permanent or not

Warren Carpenter and Boak ¹⁵⁰ note the frequency with which herpes simplex develops after a therapeutic induction of fever During one period in 1933 extensive symptomatic herpes and mild symptoms of meningoencephalitis developed in each of 15 treated patients Since 1936 the syndrome has appeared in only a few patients In general, 42 per cent of all patients observed after fever treatment have had herpes A much smaller number 7 per cent, have had herpes after subsequent fever treatments, suggesting the establishment of immunity The authors assume that the elevation of temperature provided the stimulus for the activity of the virus which is usually present in a latent state in the patient It seems likely that the virus is present not only in the saliva but in other secretions, and in tissues as well

Findlay and MacCallum ¹⁵¹ describe a case of "traumatic" herpes, in which herpes developed at the site of an injury on a child's finger Herpes they believe, may be implanted on the skin, especially with saliva Relapses often occur in spite of the presence of immune bodies The site of residence of the virus during the latent period is unknown

Poliomyelitis—The manner of transmission of poliomyelitis is a subject of much controversy Three routes are under investigation, the nasal pathway the gastrointestinal route, and the cutaneous route associated with infection by mosquitoes Some observers ¹⁵² believe it more logical at present to regard poliomyelitis as an intestinal disease than as

148a Armstrong, C, Wallace, J J, and Ross, L Lymphocytic Choriomeningitis Gray Mice *Mus Musculus*, a Reservoir for the Infection, Pub Health Rep 55 1222-1229 (July 5) 1940

149 Anderson, K The Encephalitogenic Property of Herpes Virus, Science 90 497 (Nov 24) 1939

150 Warren S L, Carpenter, C M, and Boak, R A Symptomatic Herpes A Sequela of Artificially Induced Fever, J Exper Med 71.155-168 (Feb) 1940

151 Findlay, G M, and MacCallum, F O Recurrent Traumatic Herpes, Lancet 1 259-261 (Feb 10) 1940

152 Paul J R, Trask, J D, and Vignec, A J New Aspects of the Clinical Epidemiology of Poliomyelitis, Tr A Am Physicians 54.119-122, 1939

one entering through the respiratory tract King¹⁵³ points out that the strains of virus are variable and that actually little is known about the interaction between virus and nerve tissue. In experimental studies, viruses which enter by the olfactory route seem to have a special ability to do so. Strains freshly isolated may be infective when inoculated subcutaneously, but this property is readily lost on aging. There is little evidence in the naturally occurring disease that the virus passes directly from the nasal mucous membrane by way of the olfactory neurons to the brain. In replying to the discussion of his paper, King^{153a} states that a purely neurotropic virus is probably nonexistent. Most virus infections are systemic diseases, and the involvement of the nervous system may be the predominant feature or only a minor one. Both he and Sabin¹⁵⁴ discuss the problems of the local and constitutional barriers against infection of the nervous system by filtrable viruses. Sabin^{154a} suggests that the presence or absence of certain factors either in the maternal diet during the nursing period or in the diet of actively growing young mice can promote, retard or inhibit the development of at least one type of constitutional barrier.

Paul, Trask and Culotta¹⁵⁵ demonstrated the presence of the virus of poliomyelitis in appreciable quantities in sewage from a city during an epidemic. These studies, in addition to previous ones¹⁵⁶ in which the virus was isolated from feces of patients and healthy contacts, and a subsequent one¹⁵⁷ in which statistical evidence pointed to a predominance of the disease in communities without adequate sewage disposal, add great weight to the theory that poliomyelitis enters and leaves the body through the gastrointestinal tract. It has also been suggested that the virus may enter through the nasal passages on bathing in water polluted with sewage¹⁵⁸. Chlorine in a concentration of 0.5 part per million

153 King, L. S. Some Problems in the Pathology of Neurotropic Viruses. *J. A. M. A.* **113** 1940-1945.

153a King,¹⁵³ p. 1946.

154 Sabin, A. B. Constitutional Barriers to Involvement of the Nervous System by Certain Viruses, *Science* **91** 84-87 (Jan. 26) 1940.

154a Sabin, A. B. Nutrition as a Factor in the Development of Constitutional Barriers to the Involvement of the Nervous System by Certain Viruses, *Science* **91** 552-554 (June 7) 1940.

155 Paul, J. R., Trask, J. D., and Culotta, C. S. Poliomyelitis Virus in Sewage, *Science* **90** 258-259 (Sept. 15) 1939.

156 Kramer, S. D., Gilliam, A. G., and Molner, J. G. Recovery of Virus of Poliomyelitis from Stools of Healthy Contacts in an Institutional Outbreak, *Pub. Health Rep.* **54** 1914-1922 (Oct. 27) 1939.

157 Casey, A. E., and Aymond, B. J. The Distribution of Poliomyelitis in Louisiana, *Science* **91** 17-18 (Jan. 5) 1940.

158 Ellsworth, S. M. Can Infantile Paralysis Be Spread by Bathing in Sewage-Polluted Water? *New England J. Med.* **222** 52-58 (Jan. 11) 1940.

which is greater than the concentration usually attained in municipal water purification, did not inactivate the virus of poliomyelitis^{158a}

Previous suggestions incriminating the mosquito as a vector of poliomyelitis receive no support from the work of Cornell and Davis,¹⁵⁹ who were unable to demonstrate the virus in mosquitoes which fed on a monkey suffering from the disease. That air currents or mosquitoes may be a factor in the spread of poliomyelitis is suggested by Murphy¹⁶⁰ from a geographic study of the peculiar distribution of cases in Nebraska. But a Canadian observer¹⁶¹ encountered 4 cases, said to be instances of poliomyelitis, in November and in January 1939, which would seem not to support the theory of an insect vector unless one also introduces the possibility of long latency of infection after inoculation.

An important contribution to the experimental study of poliomyelitis was made by Armstrong,¹⁶² who successfully established a strain of virus in the eastern cotton rat and subsequently in white mice. Whether this strain of virus alone or all strains are pathogenic for these conveniently handled animals is as yet unknown.

Rabies—A great amount of interest has been revived in the study of rabies. An answer to a query¹⁶³ in *The Journal of the American Medical Association* advised against cauterization of wounds as an antiquated preventive measure, washing with soap and water and irrigation were said to suffice unless the wound was deep or irregular, in the latter case the wound should be opened or enlarged, to insure thorough cleansing, after which if indicated, Pasteur's method of treatment should be instituted. Two physicians¹⁶⁴ take exception to the advice against cauterization of the wound and are answered by the Editor, who supports the advice given by referring to experiments which show how rapidly particulate matter is carried away from soft tissues by lymph. If this is

158a Kempf, J. E., and Soule, M. H. Effect of Chlorination of City Water on Virus of Poliomyelitis, *Proc Soc Exper Biol & Med* **44** 431-434 (June) 1940

159 Cornell, V. H., and Davis, W. A. Mosquito Transmission Experiment with Poliomyelitis Virus, *Proc Soc Exper Biol & Med* **42** 78-80 (Oct) 1939

160 Murphy, J. H. Comparative Epidemiology of Encephalomyelitis and Poliomyelitis, *Nebraska M J* **24** 453-458 (Dec) 1939

161 McGugan, A. C. Outbreak of Acute Anterior Poliomyelitis in Alberta During the Winter Season, *Canad Pub Health J* **30** 495-499 (Oct) 1939

162 Armstrong, C. Experimental Transmission of Poliomyelitis to the Eastern Cotton Rat, *Sigmodon Hispidus Hispidus*, *Pub Health Rep* **54** 1719-1721 (Sept 22) 1939, Successful Transfer of the Lansing Strain of Poliomyelitis Virus from the Cotton Rat to the White Mouse, *ibid* **54** 2302-2305 (Dec 29) 1939

163 Dog Bites and Rabies, Queries and Minor Notes, *J A M A* **112** 1283 (April 1) 1939

164 Dog Bites and Rabies, Queries and Minor Notes, *J A M A* **113** 1434 (Oct 7) 1939

the case with rabies virus, which it most likely is, there is no justification for the deliberate destruction of tissue with escharotics in the vain hope of preventing the spread of the infection, even after only a few minutes have elapsed since the virus was inoculated Gloyne,¹⁶⁵ Kellogg¹⁶⁶ and Denison and Dowling¹⁶⁷ strongly support the use of nitric acid to cauterize the wound The question obviously is unsettled

Denison and Dowling¹⁶⁷ in a carefully prepared paper describe their experiences in Birmingham, Ala., and set forth clear indications as to when to give and when not to give vaccine treatment They recall the hysteria and the resultant errors in judgment regarding the use of vaccine, which often lead to wastefulness in giving it to persons who do not need it The harm which may follow as a result of numerous complications of vaccine treatment must also be considered

They emphasize that the value of vaccine treatment as a life-saving measure is exaggerated Of 48 persons who died of rabies, 23 or 48 per cent, were judged to have had prompt and adequate treatment Ratchliffe,¹⁶⁸ in Indiana, found that 12 of 40 patients who died had received the Pasteur treatment and that the duration of the disease in the treated patients did not differ from that in the untreated ones In 4 of 6 fatal cases studied by Leach and Johnson,¹⁶⁹ Pasteur treatment had been given early

The Birmingham observers¹⁶⁷ point out the rarity of the disease in man as compared with its frequency among dogs (1 per cent), it is therefore not easily contracted Nevertheless, because of its great danger, patients receiving bites and scratches from rabid animals should always be treated with vaccine, in spite of the hazard of vaccine paralysis or other serious complications of the treatment itself The problem of the control of rabies, they state, appears to be one of home-owned pets and not particularly of unidentified stray dogs

Health officers of Los Angeles¹⁷⁰ criticize the paper of Denison and Dowling as dangerous in overemphasizing the deficiencies in treatment

165 Gloyne, L Dog Bites and Rabies, Correspondence, *J A M A* **113** 1752 (Nov 4) 1939

166 Kellogg, W H Treatment of Bites of Rabid Animals, Correspondence, *J A M A* **114** 910 (March 9) 1940

167 Denison, G A, and Dowling, J D Rabies in Birmingham, Alabama Human Mortality as Affected by Antirabies Treatments, *J A M A* **113** 390-395 (July 29) 1939

168 Ratchliffe, A W Rabies in Indiana Survey 1926 to June 1938, with Analysis of Human Deaths, *J Indiana M A* **32** 366-371 (July) 1939

169 Leach, C N, and Johnson, H N Human Rabies with Special Reference to Virus Distribution and Titer, *Am J Trop Med* **20** 335-340 (March) 1940

170 Pomeroy, J L, and Swartout, H O Rabies, Correspondence, *J A M A* **113** 1898-1899 (Nov 18) 1939

and object to their statistical analysis. In defense Denison and Dowling¹⁷¹ reply, with justification, I believe, that any reflection on the efficacy of antirabies vaccine renders the control of dogs even more important.

Webster¹⁷² reviewed the literature concerning antirabies immunization and, contrary to expectations, found a surprisingly meager amount of evidence supporting the use of vaccine. The published results are generally inconsistent and nonquantitative. Pasteur's tests on the immunization of dogs, for example, have not been confirmed. Over a period of fifty years only 1 of 10 investigators, Fermi, obtained definite protection *after* virus had been introduced, and the amount of vaccine given his animals was at least 25 per cent of the body weight. Even Fermi's work is unconfirmed. The results of other experiments were slightly more hopeful but only when vaccine was given *before* infection. The results of the experiments in general are irregular and show not only meager immunizing power in vaccines but little superiority of one preparation or procedure over another. Webster¹⁷³ describes a reliable method whereby the potency of antirabies virus may be tested in mice.

Kelser¹⁷⁴ in a review of the subject points out that rabies develops in only about 25 per cent of persons bitten by rabid dogs. On this basis any form of preventive measure used may be credited with 75 per cent efficacy, irrespective of whether or not its effect was specific. In spite of this fact it can be concluded from published statistics that vaccine, even of low potency, will prevent the disease in a certain proportion of the 25 per cent of cases just referred to.

It is clear that the problem of the prevention and treatment of rabies is far from being settled and is in need of further investigation. Far too much reliance is placed on the life-saving power of antirabies vaccine, partly because of the favorable statistics shown in data published by the League of Nations, yet it should be used when definitely indicated. It is far better to control the disease at its source—namely, among dogs.

Interesting observations in Venezuela¹⁷⁵ show that a form of rabies causing paralysis in livestock may be transmitted by blood-sucking vampire bats. Bats themselves suffer no ill effects. According to Good-

171 Denison, G. A., and Dowling, J. D. Rabies in Alabama, Correspondence, *J. A. M. A.* **114** 76-77 (Jan. 6) 1940.

172 Webster, L. T. The Immunizing Potency of Antirabies Vaccines. A Critical Review, *Am. J. Hyg. (Sect. B)* **30** 113-134 (Nov.) 1939.

173 Webster, L. T. A Mouse Test for Measuring the Immunizing Potency of Antirabies Vaccines, *J. Exper. Med.* **70** 87-106, 1939.

174 Kelser, R. A. The Epidemiology and Prophylaxis of Rabies, Virus and Rickettsial Diseases, Cambridge, Mass., Harvard University Press, 1940, pp. 642-660.

175 Iturbi, J., and Gallo, P., abstracted, *Science (supp.)* **91** 12 (May 24) 1940.

pasture,^{175a} Dawson modified a strain of rabies virus by passage through chick embryos, so that it caused only self-limited encephalitis in rabbits but left solid immunity to a heavy dose of "street" virus

Smallpox Vaccine—Donnelly¹⁷⁶ compared the relative merits of calf lymph virus and the new culture vaccine virus of Rivers. Both types of vaccine evoke similar skin reactions in babies when injected intradermally. However, when immunity was tested by revaccination, 73 per cent of 34 infants vaccinated with calf lymph virus were immune as compared with only 5.5 per cent of 36 children vaccinated with culture virus lymph. It is uncertain, of course, whether immunity to revaccination is as satisfactory a test as immunity to spontaneous infection, but it is unfortunate that the culture virus is not more efficacious, since it has a number of advantages over calf lymph virus.

In the experience of Ellis and Boynton,¹⁷⁷ calf lymph virus gave a higher percentage of primary "takes" among university students than culture virus vaccine. Local and constitutional reactions were somewhat less with Goodpasture's vaccine than with calf lymph material, but Rivers's vaccine frequently gave constitutional reactions when inoculated intracutaneously.

A comment in the *Public Health Reports*¹⁷⁸ emphasizes the necessity of rigid enforcement of vaccination as a preventive measure against smallpox. In New Jersey, where vaccination is common, with a population of 4,400,000 no smallpox has been reported in seven years, in seven western states where vaccination is loosely enforced, 12,000 cases were reported in the same period in a smaller population.

More evidence has been given that vaccinia represents a "degraded" virus of variola, a virus which has lost a specific antigen.¹⁷⁹ Its virulence for man is diminished, but a wider range of infectivity for different animal species is gained. Cross immunity between vaccinia and variola, though strong, is not completely reciprocal. Protection induced by vaccinia is complete against both viruses, but that of variola is complete

175a Goodpasture, E. W. Immunity to Virus Diseases, *New England J. Med.* **222** 901-910 (May 30) 1940

176 Donnelly, H. H. Smallpox Vaccination of Infants. Revaccination After Two to Three Years in Children Primarily Vaccinated with Culture Virus (Rivers), Compared with Those Primarily Vaccinated with Calf Lymph Virus, *J. A. M. A.* **113** 1796-1800 (Nov. 11) 1939

177 Ellis, R. V., and Boynton, R. E. Smallpox Vaccination. Comparison of Vaccines and Technics, *Pub. Health Rep.* **54** 1012-1025 (June 9) 1939

178 Why Smallpox? *Pub. Health Rep.* **54** 1091-1092 (June 23) 1939

179 Horgan, E. S., and Haseeb, M. A. Cross Immunity Experiments in Monkeys Between Variola, Alastrim and Vaccinia, *J. Hyg.* **39** 615-637 (Nov) 1939

only against itself and usually complete against vaccinia. Complete immunity is largely dependent on the intensity of the primary reaction.

Psittacosis—Meyer and Eddie¹⁸⁰ have devised a complement fixation test which they claim is an invaluable aid in the early and late diagnosis of psittacosis.

FOOD POISONING

Botulism—Watson¹⁸¹ reports an outbreak of botulism in Seattle. Sixteen patients were studied. They were treated with botulinus antitoxin, and 5 died, a mortality rate of about 30 per cent. Watson holds that the use of antitoxin is imperative in all cases regardless of the duration of symptoms or of the length of the incubation period, a stand with which most physicians will agree, since treatment with antitoxin is the only specific therapy available. On the other hand, the number of cases reported is far too small for one to conclude with Watson that this treatment was responsible for the low mortality rate. One feels that much more knowledge of the problem is necessary. Studies similar to the ones of Abel and his associates on tetanus should be made to determine whether or not botulinus antitoxin can attack or neutralize toxin already absorbed. The paper contains detailed instructions as to the use of antitoxin, artificial respiration and other means of treatment.

A few studies have been made in this country on the subject. Recently Schneider and Fisk¹⁸² were able to demonstrate the toxin in the blood in 1 fatal case and in extracts of the liver in 2 others. Toxin was present in one liver even though 10,000 units of antitoxin (A and B) had been given five hours before death. No toxin was found in the blood of 3 patients who recovered. The demonstration of the toxin is a valuable aid in diagnosis.

Toxemia from Salmonella—Two localized outbreaks of food poisoning caused by "Salmonella newport" have been described. In 1 case¹⁸³ liver paste was probably contaminated during its preparation by unhygienic methods.

Another interesting study of an outbreak caused by *Salmonella aertrycke* was made in Kansas¹⁸⁴. Contaminated food served in an

180 Meyer, K. F., and Eddie, B. The Value of the Complement Fixation Test in the Diagnosis of Psittacosis, *J. Infect. Dis.* **65** 225-233 (Nov-Dec) 1939.

181 Watson, W. E. Treatment of Botulism, *Northwest Med.* **38** 382-387 (Oct) 1939.

182 Schneider, H. J., and Fisk, R. Botulism. Demonstration of Toxin in Blood and Tissues, *J. A. M. A.* **113** 2299-2300 (Dec 23) 1939.

183 Andrew, D. H., Korff, F. A., and Ewing, C. L. Two Related Outbreaks of Food Poisoning Attributed to a *Salmonella* Organism, *J. A. M. A.* **113** 2300-2302 (Dec 23) 1939.

184 Brown, E. G., Combs, G. R., and Wright, E. Food-Borne Infection with *Salmonella Aertrycke*, *J. A. M. A.* **114** 642-644 (Feb 24) 1940.

orphanage made 52 out of a group of 71 persons sick, some of them seriously and 1 died. The source of the trouble was traced to pudding made with duck eggs. Duck eggs are especially liable to infection with *Salmonella* since they are usually laid in wet places contaminated with feces, and *Salmonella* are known to be able to enter the egg through the intact shell. Moreover, the egg may harbor the bacteria from its earliest stage, probably as a result of infection of the oviduct during copulation. In the outbreak studied, *S. aertrycke* was recovered from the feces of 9 ducks on the premises, and the blood of 3 agglutinated these bacilli. Similar bacteria were also recovered from the pudding and from the feces of 17 patients. Whether the bacilli were habitually present in the ducks or were introduced into the flock by infected excrement from a caretaker who was sick with a similar disease a week earlier is unknown, but I should favor the former possibility. The caretaker also probably ate duck eggs.

RICKETTSIAL DISEASES

Topping and Dyer¹⁸⁵ isolated a strain of the rickettsias of Rocky Mountain spotted fever from a patient near Washington, D. C., which resembles in all respects the typical virulent so-called western type. The terms "eastern" and "western," therefore, are apparently no longer useful, it may be better to classify various strains on the basis of virulence or of behavior in inoculated guinea pigs.

Parker,¹⁸⁶ testing ticks incident to a survey of possible disease-carrying ticks in Texas, encountered two strains of an infectious agent pathogenic to guinea pigs. These strains caused fever, scrotal edema and reddening, splenomegaly and immunity to subsequent infection. They seem gradually to lose virulence during transfer from animal to animal, and can be maintained only by repeated passage of testicular washings. Although a degree of cross immunity with Rocky Mountain spotted fever, boutonneuse fever and endemic typhus fever is established, the temperature reaction to the newly discovered infection is shorter and lower than that to any of the infections just named. The rickettsia-like bodies which were found resembled those of Rocky Mountain spotted fever.

Cox¹⁸⁷ reports further experiments on the newly isolated *Rickettsia diaporica* so named because it can be passed through a porcelain filter.

185 Topping, N. H., and Dyer, B. E. A Highly Virulent Strain of Rocky Mountain Spotted Fever Virus Isolated in the Eastern United States, *Pub. Health Rep.* **55** 728-731 (April 26) 1940.

186 Parker, R. R. Observations on an Infectious Agent from *Amblyomma maculatum*. *Pub. Health Rep.* **54** 1482-1484 (Aug. 11) 1939.

187 Cox, H. R. Studies of a Filter-Passing Infectious Agent Isolated from Ticks, *Pub. Health Rep.* **54** 1822-1827 (Oct. 6) 1939.

Because of this property it should perhaps be classified as a new genus, differing from other rickettsias. Three more strains were collected in Wyoming and studied by Davis¹⁸⁸

Lewthwaite and Savooi¹⁸⁹ give a detailed description of tsutsugamushi disease and show that it is the same as "rural typhus," "scrub typhus" and "Sumatran mite fever." The latter terms are therefore redundant and should be abolished.

The engineering methods for the control of rats and murine typhus are described by Boston^{189a}

Rickettsial Vaccines—In a short paper reviewing the development of rickettsial vaccines, Zinsser and his assistants¹⁹⁰ report a new technic for producing vaccine against the epidemic form of typhus on a large scale. Typhus rickettsias grown in eggs are transferred to minced chick tissue cultures for growth. Subcultures are subsequently spread on the surface of relatively large expanses of agar in modified Kolle flasks for growth and later harvesting. A team of 3 persons can make sufficient vaccine in a week for 300 immunizations.

A vaccine has been prepared by Cox and Bell¹⁹¹ which protects guinea pigs from infection with the endemic (murine) form of typhus. Clinical trials are about to be made. They also report the preparation of a vaccine capable of protecting guinea pigs against epidemic typhus, but it is not so effective as that against the endemic variety.

Fitzpatrick¹⁹² vaccinated 2 monkeys subcutaneously with formal-dehydized "tissue culture" typhus rickettsia vaccine. Neither showed the Weil-Felix reaction, but both had low agglutinin titers for rickettsias after several weeks, and both were immune to inoculation with live typhus rickettsias. In contrast, typical typhus fever developed in an unvaccinated monkey, together with a Weil-Felix reaction titer of 1:640 and a rickettsia agglutination titer of 1:1,280. A vaccine of eastern

188 Davis, G. E. *Rickettsia Diaporica*. Recovery of Three Strains from Dermacentor Andersoni Collected in Southeastern Wyoming, Their Identity with Montana Strain 1, Pub Health Rep **54** 2219-2227 (Dec 15) 1939.

189 Lewthwaite, R., and Savooi, S. R. *Rickettsia Diseases of Malaya*. Identity of Tsutsugamushi and Rural Typhus, Lancet **1** 255-259 (Feb 10) 1940.

189a Boston, R. J. Public Health Engineering Phases of Murine Typhus Control, Am J Pub Health **30** 619-626 (April) 1940.

190 Zinsser, H., Plotz, H., and Enders, J. Mass Production of Vaccine Against Typhus Fever and of the European Type, Science **91** 51-52 (Jan 12) 1940.

191 Cox, H. R., and Bell, E. J. Epidemic and Endemic Typhus. Protective Value for Guinea Pigs of Vaccines Prepared from Infected Tissues of the Developing Chick Embryo, Pub Health Rep **55** 110-115 (Jan 19) 1940.

192 Fitzpatrick, F. K. Vaccination of Monkeys with Agar-Tissue Cultures of European Rickettsia, Proc Soc Exper Biol & Med **42** 217-218 (Oct) 1939, Vaccination Against Spotted Fever with Agar-Tissue Cultures, ibid **42** 219-220 (Oct) 1939.

type Rocky Mountain spotted fever prepared in the same manner protected guinea pigs against spotted fever

After unsuccessful trials by others, Topping¹⁹³ was able to make an antiserum which protects a large majority of guinea pigs and monkeys against experimental infection with ticketsias of Rocky Mountain spotted fever. The serum was prepared by vaccinating rabbits first with formaldehydized vaccine and then with small but gradually increasing doses of active tick virus.

Malaria—The Fondes¹⁹⁴ point out facts concerning malaria which most physicians not familiar with the disease seldom realize. The first is the importance of chronic malaria as comprising the majority of cases of malaria. It is easy enough to recognize the "classic" acute disease, with its regularly spaced paroxysms, splenomegaly and parasites in the blood, but the more widespread chronic form with its protean manifestations is easily mistaken for other diseases. Another point is that the malaria infection, like that of tuberculosis, syphilis, undulant fever, tularemia and others, is a tenacious one, persisting for years in spite of specific therapy. Specific therapy, it seems merely renders the infection asymptomatic, somewhat, perhaps, in the way that the salicylates influence the symptoms but not the underlying infection in rheumatic fever. The authors refer to the recent important work of James and Tate, who demonstrated the existence of the vegetative cycle in the animal body, and of Tahaferio and Cannon, who showed that phagocytic activity renders the disease asymptomatic in spite of the fact that the parasites reproduce at the same rate. The authors rightly deplore the use of "standardized" procedures in treating the disease and outline a rational scheme of prevention and treatment.

The pessimistic or perhaps realistic views just stated are supported by the disillusioning conclusion of Scott¹⁹⁵. He writes "malaria in warm climates is as bad, as rife, as prevalent as ever and nearly as fatal as it was a quarter of a century ago," in spite of the amount of knowledge physicians have of the disease.

An excellent review of infectious mononucleosis was published by Bernstein¹⁹⁶ and of coccidiomycosis by Smith^{196a}.

193 Topping, N. H. Treatment of Infected Laboratory Animals with Immune Rabbit Serum, Pub. Health Rep. **55** 41-46 (Jan. 12) 1940.

194 Fonde, G. H., and Fonde, E. C. Chronic Malaria. A Clinical Consideration, Arch. Int. Med. **64** 1156-1169 (Dec.) 1939.

195 Scott, H. H. A History of Tropical Medicine Based on the Fitzpatrick Lectures Delivered Before the Royal College of Physicians of London, 1937-1938, Baltimore, William Wood & Company, 1939.

196 Bernstein, A. Infectious Mononucleosis, Medicine **19** 85-159 (Feb.) 1940.

196a Smith, C. E. Epidemiology of Acute Coccidiomycosis with Erythema Nodosum ("San Joaquin" or "Valley Fever"), Am. J. Pub. Health **30** 600-611 (April) 1940.

UNUSUAL AND RARE DISEASES

Leptospirosis—From studies carried on chiefly in Europe, leptospirosis seems to be far more common and widespread than is at present believed. A disease or group of diseases called mud fever, swamp fever, field fever or harvest fever is often seen in such widely separated places as Germany, Russia, Italy,¹⁹⁷ Japan and Sumatra. Hundreds of harvesters had field fever one summer in Bavaria.¹⁹⁸ The disease in some places is caused by a spirochete called *Leptospira grippotyphosa*, and in others by *Leptospira hebdomidis* or *Leptospira canicola*, each of which is indistinguishable morphologically from the *Leptospira icterohaemorrhagiae* of Weil's disease. Rimpau¹⁹⁹ and others regard the infections as similar to Weil's disease, or the nonicteric form of it, since jaundice is present in less than 2 per cent of patients as compared with about 50 per cent in Weil's disease. It is my own feeling that jaundice is present in far less than 50 per cent of the cases if all mild cases of Weil's disease are included in the statistics. Because of the sudden onset, with high fever, conjunctival injection, severe headache, dizziness and aching of the limbs, mild attacks of leptospirosis without jaundice are often mistaken for influenza. The mortality from the other leptospiroses seems to be lower than that from Weil's disease. Joerdens¹⁹⁸ reports favorable results from treatment with specific immune serum. The best recent review of the subject is by Walch-Sorgdrager,²⁰⁰ who also discusses prophylaxis with specific vaccines.

The close relationship of the micro-organisms causing mud, field or harvest fever to *L. icterohaemorrhagiae* and their serologic differences from this *Leptospira* are shown in studies by Karakašević.²⁰¹ A strain of leptospiroses of rice field fever, according to Babudieri,^{201a} was less virulent for guinea pigs than *L. icterohaemorrhagiae* and caused only multiple punctate hemorrhages in the lungs. The strain he studied was identical with *Leptospira bataviae* from Java, where the disease, as in Italy, occurs in rice harvesters.

The fact that jaundice is not a regular feature of Weil's disease may account for the probability that many cases are unrecognized in the

197 Mino, P. Ueber Leptospirose bei den Arbeitern der Reisfelder Oberitaliens, *Ztschr f Immunitätsforsch u exper Therap* **96** 466-520 (Oct 2) 1939

198 Joerdens, G. Beitrag zur Klinik und spezifischen Serumtherapie des Feldfiebers, *München med Wchnschr* **85** 1979-1981 (Dec 23) 1938

199 Rimpau, W. Weiteres zur Epidemiologie des Feldfiebers in Sudbayern, *München med Wchnschr* **85** 1977-1979 (Dec 23) 1938

200 Walch-Sorgdrager, B. Leptospirose, *Bull Health Organ League of Nations* **8** 143-386, 1938

201 Karakašević, B. Serologische Untersuchungen über die Spirochete des Feldfiebers ("*Spirochaeta grippo-typhosa*"), *Ztschr f Immunitätsforsch u exper Therap* **96** 427-439 (Oct 2) 1939

201a Babudieri, B. *R C Ist san pubbl*, December 1939, p 755

United States Since 1922 only 23 cases have been reported in American literature, in contrast with 248 in the British Isles²⁰² and 21 in Norway²⁰³ since 1936 Many cases in this country are recognized but not reported Havens and his associates²⁰⁴ report the first instance in the United States of a small outbreak of Weil's disease in bathers This occurred among 7 young men and was caused by swimming in a contaminated pool The vicinity of the pool was infested with rats, the probable source of the infection Two of the patients were severely ill, 1 of these died, the rest had mild attacks which ordinarily would not be diagnosed as Weil's disease

Reticuloendothelial Cytomycosis (Histoplasmosis of Darling)—Several more cases of cytomyces or histoplasmosis observed in the United States were reported from Washington, D C,²⁰⁵ Richmond Va,²⁰⁶ and Michigan²⁰⁷ As with many other supposedly rare diseases, it is probable that the disease occurs more commonly but is misdiagnosed One case²⁰⁵ was that of a girl whose illness began at 6 months of age, shortly after cow's milk was first used in feeding her The disease lasted six months and was characterized by drowsiness, diarrhea and constipation, hepatomegaly, splenomegaly, fever and leukopenia Parasitic bodies resembling Leishmania were found in large endothelial cells of the skin, liver, spleen, pancreas, intestine, lymph nodes, adrenal and bone marrow The organism was first thought to belong to Leishmania, but others believe it to be one of the fungi imperfecti Its true position is uncertain

De Monbreun²⁰⁸ found *Histoplasma capsulatum* the cause of the disease in the tissues of a dog, which is the first time the micro-organism has been discovered outside of man He suggests that the dog may be the natural host of the disease, which may be spread to man by way

202 Alston, J M Leptospirosis in the British Isles, abstracted, Report of the Proceedings of the Third International Congress for Microbiology, New York, Sept 2-9, 1939, New York, The Congress, 1940, p 638

203 Thjotta, T, and Borgen, L Leptospira Infection in Norway abstracted Report of the Proceedings of the Third International Congress for Microbiology, New York, Sept 2-9, 1939, New York, The Congress, 1940, p 639

204 Havens, W P, Bucher, C J, and Reimann, H A Leptospirosis A Public Health Hazard, Report of a Small Outbreak in Bathers, J A M A, to be published

205 Shaffer, F J, Shaul, J F, and Mitchell, R H Histoplasmosis of Darling, J A M A **113** 484-488 (Aug 5) 1939

206 Reid, J D, Scherer, J H, and Irving, H Systematic Histoplasmosis in the United States, Science **91** 264 (March 15) 1940

207 Humphrey, A A Reticuloendothelial Cytomycosis (Histoplasmosis of Darling), Arch Int Med **65** 902-918 (May) 1940

208 De Monbreun, W A The Dog as a Natural Host for *Histoplasma Capsulatus*, Am J Trop Med **19** 565-582 (Nov) 1939

of excieta By an unusual coincidence, Chinese investigators in Peiping, China,²⁰⁹ also decided that dogs were an important factor in the spread of canine leishmaniasis Sandflies could be infected by feeding on dogs with cutaneous lesions It is as yet uncertain whether canine and human leishmaniasis are identical, but dogs could be infected with material from human patients, furthermore, human kala-azar and canine leishmaniasis have been found in the same household

The similarity of the conclusions reached by investigators in the United States and in China seems to me to favor the view that the micro-organisms of histoplasmosis belong in the group of *Leishmania* and not in that of the fungi Clinically, the course of the disease is much more like that found in leishmaniasis than in fungous infections, yet De Monbreun and others have demonstrated the formation of mycelia in cultural studies and have transferred the disease to monkeys Humphrey²⁰⁷ believes the micro-organism to be unquestionably a fungus I doubt that increased facilities for transportation accounts for the spread of the disease and the increasing number of recognized cases, as Humphrey suggests

Yuan and his associates²¹⁰ feel that the development of kala-azar in young infants chiefly in the early summer months, at the time when sandflies are most prevalent, suggests that these insects may be important transmitters of the disease

Toxoplasmosis—Wolf, Cowen and Paige²¹¹ report the fifth human case of granulomatous encephalomyelitis caused by a protozoon, *Toxoplasma* The disease affects young infants and gives evidence of generalized involvement of the nervous system with miliary granulomas There may be ophthalmoscopically identifiable lesions in the ocular fundi In a later paper²¹² they report the transfer of the infection to rabbits and mice The morphologic aspects of the organisms in the human and in the animal lesions were identical They suggest *Toxo-*

209 Feng, L C, Chung H L, and Hoeppli, R Canine Leishmaniasis with Skin Lesions Observed in Peiping, Chinese M J **55** 371-378 (April) 1939 Ho, E A A Note on the Coincidence of Human Kala-Azar and Canine Leishmaniasis with Cutaneous Lesions in a Household, *ibid* **55** 566-567 (June) 1939 Feng, L C, and Chung H L The Development of *Leishmania* in Chinese Sandflies Fed on Dogs with Canine Leishmaniasis, *ibid* **56** 35-46 (July) 1939

210 Yuan, I C, Chu, F T, and Lee, C V Seasonal Incidence of Kala-Azar in Infants and Its Significance in Relation to the Transmission Problem of the Disease, Chinese M J **56** 241-264 (Sept) 1939

211 Wolf, A, Cowen, D, and Paige, B H Toxoplasmic Encephalomyelitis A New Case of Granulomatous Encephalomyelitis Due to a Protozoon, Am J Path **15** 657-694 (Nov) 1939

212 Wolf, A, Cowen, D, and Paige, B H Toxoplasmic Encephalomyelitis IV Experimental Transmission of the Infection to Animals from a Human Infant, J Exper Med **71** 187-214 (Feb) 1940

plasma hominis as its name Pinkerton and Weinman,^{212a} after giving a historical review of the subject report the first authentic case of toxoplasmosis in an adult and methods for the diagnosis and identification of the organism

Miscellaneous—Several unusual cases of endocarditis were studied In one,²¹³ endocarditis occurred in a patient with erysipeloid Erysipeloid in itself is an interesting disease, caused by *Erysipelothrix rhusiopathiae* and is most commonly found among fishermen and workers in abattoirs It is known to the laity as "fish poisoning" The etiologic agent causes a similar disease, swine erysipelas (*Schweineotlauf*), with endocarditis, in animals In the other cases the endocarditis was caused by peculiar gram-negative cocci²¹⁴

A rare case²¹⁵ of abscess of the liver caused by Friedlander's bacilli and a case²¹⁶ of peritonitis caused by *Coccidioides immitis* were observed Two cases of meningitis with recovery, caused by *Micrococcus tetragenus*, are reported²¹⁷

In the past few years several remarkable examples of excellent observation and association of facts have clarified the knowledge concerning important diseases involving both man and animals For example, Alice Evans recognized and proved the relationship and identity of the microbes of Bang's disease of cattle and human brucellosis In a similar manner, Francis in 1919 showed that deer fly fever and a plague-like disease of rodents were both caused by *Pasteurella tularensis* and gave the disease its name, tularemia

Recently more mystery and confusion have been cleared up A relationship has been discovered in the cause of four diseases heretofore unassociated with one another, namely, (a) a form of rat bite fever (b) Haverhill fever, (c) a cattle disease, pleuropneumonia, and (d) a disease of rats studied by Woglom A number of years ago several

212a Pinkerton, H, and Weinman D Toxoplasma Infection in Man Arch Path **30** 374-392 (July) 1940

213 Russell, W D, and Lamb, M E Erysipelothrix Endocarditis A Complication of Erysipeloid, Report of a Case with Necropsy, J A M A **114** 1045-1050 (March 23) 1940

214 Shilling, M S Bacteriology of Endocarditis, with Report of Two Unusual Cases, Ann Int Med **13** 476-486 (Sept) 1939

215 Boettiger, C, Weinstein, M, and Werne, J Primary Suppuration of Liver Due to Friedlander's Bacillus, J A M A **114** 1050-1055 (March 23) 1940

216 Ruddock, J C, and Hope, R B Coccidioidal Peritonitis Diagnosis by Peritoneoscopy, J A M A **113** 2054-2055 (Dec 2) 1939

217 McGowan, T S, and Kisner, P A Review of Meningitis Due to Micrococcus Tetragenus, Arch Int Med **64** 15-25 (July) 1939 Criscitello, M Meningitis Due to Micrococcus Tetragenus Report of a Case with Recovery Following Treatment with Sulfanilamide, New England J Med **221** 383-385 (Sept 7) 1939

observers, notably Schottmüller (1914) and Blake (1916), reported an unusual form of disease following the bite of a rat. The causative organism seemed to be *Streptothrix muris ratti* or *Streptobacillus moniliformis*. For many years these observers were suspected of having made the mistake of isolating a saprophyte instead of the actual etiologic agent in a case of rat bite fever, or sodoku, as caused by the better known *Spirillum minus* (*Treponema moisis muris*), a disease which can be cured with arsphenamine. Subsequent facts have proved that they were correct. Sodoku, or rat bite fever, is indeed caused by a spirillum, but the disease they studied, though it followed a rat bite, was caused by a different organism. The next important observation was made in 1926, when a localized epidemic of an unusual febrile disease occurred in Haverhill, Mass. The syndrome described by Place, Sutton and Willner was called Haverhill fever. It was supposedly caused by a highly pleomorphic filamentous gram-negative organism, called *Haverhillia multiformis*. A similar disease had been reported by Levaditi in 1925. In neither of these instances were rats suspected as the source of infection.

The third link in the chain of information came with the realization that *S. moniliformis* and *H. multiformis* were similar, if not identical, micro-organisms. The subject is summarized by Farrell, Lordi and Vogel²¹⁸ and others^{218a}.

Perhaps the most intriguing of all discoveries in this field dates from Klieneberger's work after 1935. She observed that curious colonies composed of delicate bodies, which she called L organisms, commonly occurred among typical colonies of *S. moniliformis*. These new forms she regarded as unrelated symbionts. The L forms resembled very closely the minute organism associated with pleuropneumonia bovis, which is a member of a group of bacteria pathogenic for animals. In their properties these micro-organisms differ in a number of ways from commonly known bacteria and often pass through porcelain filters.

Subsequent to these studies, Dienes²¹⁹ and Dawson²²⁰ modified the interpretation of Klieneberger and showed that the pleuropneumonia-like bacteria were not unrelated symbionts but actually a variant of

218 Farrell, E., Lordi, G. H., and Vogel, J. Haverhill Fever. Report of a Case with Review of Literature, *Arch. Int. Med.* **64** 1-14 (July) 1939.

218a Albritten, F. F., Sheely, R. F., and Jeffers, W. A. Haverhillia Multiformis Septicemia. Its Etiologic and Clinical Relationship to Haverhill and Rat-Bite Fevers. *J. A. M. A.* **114** 2360-2363 (June 15) 1940.

219 Dienes, L. L. Organisms of Klieneberger and Streptobacillus Moniliformis, *J. Infect. Dis.* **65** 24-42 (July-Aug.) 1939. Dienes, L., and Sullivan, E. R. Morphology and Nature of Pleuropneumonia-like Microorganisms, *Proc. Soc. Exper. Biol. & Med.* **41** 424-426 (June) 1939.

220 Dawson, M. H., and Hobby, G. L. Rat-Bite Fever, *Tr. A. Am. Physicians* **54** 329-332 1939.

S. moniliformis Transformation of one form to the other was repeatedly noted. Thus there is added more important information concerning transformations of bacterial type, the occurrence of which I noted several years ago among strains of *M. tetragenus*.

Pleuropneumonia-like organisms were for a brief period suspected of having some etiologic relations with rheumatic fever,²²¹ but subsequent work has shown otherwise. The micro-organisms supposedly isolated from patients with rheumatic fever most probably were present in the lungs of the inoculated mice used in the experiments.²²² In mice and rats inoculated intranasally with cultures pneumonia develops, and occasionally pleuritis.²²³ In my review of 1938,²²⁴ Woglom's "pyogenic virus" of rats was mentioned. This unusual agent, whose nature was undetermined at the time, was recently identified by Klieneberger²²⁵ as a pleuropneumonia-like organism. Similar micro-organisms were found in the genitalia of about one third of a small number of women whose secretions were submitted for the detection of gonococci.^{225a} Whether the pleuropneumonia-like organisms as identified by morphologic criteria were potentially pathogenic was not determined.

Sulfanilamide and neosalphenamine had no influence in curing mice of experimental infection with *S. moniliformis*, but a single injection of gold sodium thiomalate (myochrysine) was sufficient to protect them from fatal doses.²²⁶

Other interesting observations on microbial dissociation were made by Dienes,²²⁷ concerning a culture of colon bacilli. Tiny colonies were seen

221 Swift, H. F., and Brown, T. M. Attempts to Cultivate Pleuropneumonia-like Microorganisms from Rheumatic Exudates, abstracted, Reports of the Proceedings of the Third International Congress for Microbiology, New York, Sept. 2-9, 1939, New York, The Congress, 1940, p. 183. Sabin, A. B. Filtrable Mesenchymotropic Microorganisms Producing Experimental Polyarthritides and Choreiform Syndromes in Mice, *ibid.*, p. 182.

222 Sabin, A. B. Mice as Carriers of Pathogenic Pleuropneumonia-like Microorganisms, *Science* **90** 18-19 (July 7) 1939.

223 Dienes, L., and Sullivan, E. R. Pneumonia in White Mice Produced by a Pleuro-Pneumonia-like Microorganism, *Proc. Soc. Exper. Biol. & Med.* **41** 620-622 (June) 1939.

224 Reimann, H. A. Infectious Diseases, *Arch. Int. Med.* **62** 305-352 (Aug.) 1938.

225 Klieneberger, E. Studies on Pleuro-Pneumonia-like Microorganisms, L4 Organism as Cause of Woglom's "Pyogenic Virus," *J. Hyg.* **39** 260-265 (May) 1939.

225a Dienes, L. Cultivation of Pleuropneumonia-like Organisms from Female Genital Organs, *Proc. Soc. Exper. Biol. & Med.* **44** 468-469 (June) 1940.

226 Heilman, F. R. Chemotherapy in Experimental Infections Caused by *Streptobacillus Moniliformis*, *Science* **91** 366-367 (April 12) 1940.

227 Dienes, L. A Peculiar Reproductive Process in Colon Bacillus Cultures, *Proc. Soc. Exper. Biol. & Med.* **42** 773-778 (Dec.) 1939.

to be composed of long wavy filaments, showing all grades of transition into large fusiform or round bodies. In 1 instance, out of many thousand observations, the contents of the large bodies and of the filaments seemed to be composed of masses of bacilli, morphologically similar to normal colon bacilli. They may represent a special form of transformation rarely encountered in bacteriologic studies.

Further interesting work on microbic dissociation was done by Randall,²²⁸ who studied the mucoid, translucent and rough culture phases of a strain of Friedlander's bacillus. The smooth translucent forms resembled the colonies of *Escherichia coli*, and because of the production of acid and gas in certain mediums, they could not be distinguished from the *Citrobacter* group of bacteria. The serologic reactions of the original types and of the variants derived therefrom revealed strict type specificity and in some cases individual specificity with the type. These results are so similar to the ones I reported for *M. tetragenus* several years ago that a parallelism is suggested. The resemblances between apparently unrelated bacteria, such as the *Klebsiella* and the *Citrobacter* group, as just told, calls to mind other recently discovered similarities between apparently unrelated bacteria, all of which involve microbic dissociation, namely, the resemblance of certain *R. pneumococci* to *Streptococcus viridans* and of *M. tetragenus* to *Staphylococcus* and the interesting relationship of *S. moniliformis* to the pleuropneumonia-like organisms.

228 Randall, W. A. Colony and Antigenic Variation in *Klebsiella Pneumoniae* Types A, B and C, *J. Bact.* **38** 461-471 (Oct.) 1939.

News and Comment

Mississippi Valley Medical Society Contest—Dr John F Casey, visiting physician, St Elizabeth's Hospital, Boston, won the third annual Essay Contest of the Mississippi Valley Medical Society "for the best unpublished essay on a subject of practical and applicable value to the general practitioner of medicine" and will receive a cash prize of \$100, a gold medal, a certificate award and an invitation to present his essay at the annual meeting of the Mississippi Valley Medical Society Dr F Stanley Morest, Kansas City, Mo, received the second certificate of merit and Dr Charles W Pavey, Columbus, Ohio, the third Dr Casey will address the Mississippi Valley Medical Society on the subject of his winning essay, "A Study of the Use of Sulfapyridine and Sulfathiazole in Pneumonia with Particular Reference to the Treatment of Pneumonia by the General Practitioner," at Rock Island, Ill, on Sept 26, 1940 Dr Casey's paper, and probably those of Drs Morest and Pavey, will be published in the January 1941 issue of the *Mississippi Valley Medical Journal*, the society's official publication

Mississippi Valley Medical Society—The sixth annual meeting of the Mississippi Valley Medical Society will be held at the Hotel Fort Armstrong, Rock Island, Ill, Sept 25 to 27, 1940 There will be numerous lectures, demonstrations, round table discussions and short instructional courses At the annual banquet on September 26 Dr N B Van Etten, New York, President of the American Medical Association, and the presidents of the Illinois State Medical Society, the Missouri State Medical Association and the Iowa State Medical Society will be speakers

The complete program appears in the September issue of the *Mississippi Valley Medical Journal*, and further information may be secured from the secretary, Harold Swanberg, M D, W C U Building, Quincy, Ill

American Congress of Physical Therapy—The nineteenth annual scientific and clinical session of the American Congress of Physical Therapy will be held Sept 2 to 6, 1940, at the Hotel Statler, Cleveland The mornings will be devoted to an instructional seminar, and the scientific program will be presented in the afternoons and evenings The complete course consists of twelve lectures from a list of forty-eight on diversified subjects The scientific program itself consists of papers, demonstrations and motion pictures covering every branch of physical therapy There will be a separate scientific program covering subjects pertaining to the eye, ear, nose and throat

Further information may be obtained by writing directly to the American Congress of Physical Therapy, 30 North Michigan Avenue, Chicago

Bicentennial Conference at the University of Pennsylvania—A bicentennial conference will be held by the University of Pennsylvania in Philadelphia, September 16 to 20 The conference will form part of a bicentennial week program commemorating the two hundredth anniversary of the origin of the University of Pennsylvania The speakers will include more than 200 American and European scholars and leaders in various fields of science and thought

Six general fields—fine arts, humanities, medical sciences, natural sciences, social sciences and religion—will be covered by the conference, during the course of which there will be eighteen general sessions and fifty-nine symposiums

Membership in the five day conference will carry with it the privilege of attending the general sessions and symposiums and will be open without charge, on application and within the limit of accommodations, to those interested in the program

Applications for membership may be addressed to the Registrar of the Bicentennial Conference, University of Pennsylvania, Philadelphia

Book Reviews

Textbook of Pathology A Correlation of Clinical Observations and Pathological Findings By Charles W Duval, M D, and Herbert J Schattenberg, M D Price, \$8.50 Pp 681, with illustrations New York D Appleton-Century Company, 1938

The appearance of a new book on a subject about which there already exists a not inconsiderable number of textbooks requires a certain amount of explanation. The authors have given this in their preface. It is their purpose, they say, to stress "the relationship between pathologic physiology and altered tissue changes or morbid anatomy." The description of the disturbance in physiologic processes which results from a pathologic process somewhere in the body is a feature which has been completely neglected in most textbooks of pathology. The physician obtains but little help from most of the books on pathology when he wants to correlate the symptom complex or the symptoms with the underlying morbid anatomy. Duval and Schattenberg make a very excellent attempt to rectify this deficiency. In practically every section of the book, following the gross and microscopic appearance of a diseased organ, there is a subsection which is captioned "Correlation." Under this subheading there is a more or less detailed explanation for the symptoms which arise during the course of the disease, with particular emphasis on the reason for the patient's death. This subsection does much to enhance the value of the book to the physician who is not an actively practicing pathologist and who is more interested in the *why* of death than in *what* causes it.

The authors have divided the book into some twenty chapters. The first chapter has to do with exudative, proliferative and degenerative processes in disease. The next chapter is concerned with the etiology of disease and the reactions of fever, immunity, shock and anaphylaxis. After these two more or less introductory chapters the various systems of the body are taken up, in succeeding chapters, in considerable detail. Not only are the diseases dependent on pathologic changes in an organ discussed but also such disorders as the deficiency diseases, diseases of the blood and neoplasia are considered. The last chapter, of some thirty pages, has to do with the autopsy.

Succeeding each chapter is a list of references to articles which have been written on the subject in the English language. Duval and Schattenberg say that the average medical student has such a poor reading knowledge of foreign languages that it is difficult for him to make use of literature in those languages. Unfortunately, the references are neither numbered nor in alphabetical order. This makes for some confusion, when one wishes to refer to an article by Whipple, for example, it is necessary to read down the list of references until one finds the name, whereas if the names were listed alphabetically a glance at the end of the list would show the reference.

One of the very commendable features of the book is the minimization of histopathology. After all, the medical student or the practicing physician rarely has the ability to make exact histologic diagnoses, nor does the occasion particularly call for such ability. It seems regrettable that this thought was not carried out in the section on neoplasia. This is a very long chapter, of some 105 pages, and considerable detail is given concerning tumors which are extremely rare and which might confound even the skilled pathologist. However, many of these pages are of illustrations which are very helpful.

Of course certain statements made in the book are tinged somewhat by the personal reactions of the authors—for example, that the etiologic factor in pellagra is a virus. Furthermore, so rapid have been the advances in the study of the deficiency diseases and the endocrine disorders that one cannot blame the contributors if some of the statements they make have already become outdated.

Another criticism has to do with the amount of space that is given to leprosy. In view of the interest of the senior author in this condition the reason for the overattention to it is obvious. However, it does seem that a disease which attacks so few people in this country (at most not more than 50 or 60 persons yearly) hardly warrants three colored plates, eight figures and eleven pages of text.

Such criticisms are minor. Fundamentally the whole work is so excellent that the trivial objections are more than outweighed. Particularly to be praised is the very large number of excellent photomicrographs. The book can be recommended, without qualification, as a textbook, and it should be of particular value to the practitioner of medicine who wants to know the why and the wherefore of disease.

The Treatment of Rheumatism in General Practice By W S C Copeman, M D, Physician in Charge of the Department of Chronic Rheumatic Diseases, West London Hospital. Price \$4. Third edition. Pp viii + 276. Baltimore: The Williams and Wilkins Company, 1939.

Just as it always is pleasant to meet an attractive person, so it is equally pleasant to be introduced to an attractive book. "The Treatment of Rheumatism in General Practice" falls in this category.

The first edition was published in 1933. It was two hundred and fifteen pages long, it sold for \$3.25 in this country and it was highly spoken of by the critical minded. Our colleague, *The Journal of the American Medical Association* (102:397-398 [Feb. 3] 1934), gave it a very favorable review. It was pointed out that there were a few minor faults in the book, particularly omission of any bibliographic references to the eighty authors mentioned, lack of discussion of gout, the disease so regularly mistaken by American physicians for rheumatic fever or chronic arthritis, and little description of the methods available for desensitization and immunization in arthritis. But, on the whole, *The Journal* liked the book and considered it a practical small volume, distinctly useful to any one dealing with the therapy of arthritis.

The *British Medical Journal* (2:607-608 [Sept. 30] 1933) also praised the first edition and recommended it highly. This journal stated that the viewpoint of the author seemed logical and that he gave a carefully considered verdict, formed largely in the light of actual experience, on therapeutic values in rheumatism. It was noted that there were a few literary inelegances which might well be deleted in future editions.

British doctors, too, evidently appreciated the book, for a second edition was published in 1935. This was thirteen pages longer than the first edition and contained various corrections and improvements, including a discussion of gold salt, therapy in rheumatism and remarks on the use of bee venom, histamine and intravenous calcium. The reviews of this edition which appeared in the *British Medical Journal* (2:787 [Oct. 26] 1935) and in the *Lancet* (2:1280 [June 1] 1935) were complimentary. On our side of the Atlantic the second edition made only a few friends, for apparently we were slow to appreciate its basic soundness. The *American Journal of the Medical Sciences* (190:273 [Aug.] 1935) said, however, what all who became acquainted with the book must have felt: that here was a book which was bound to be useful to many a perplexed practitioner who had the good fortune to have it fall into his hands.

The third edition is a little grander than its predecessors—sixty-one pages longer than the first edition and 75 cents more expensive. It runs true to form and continues to give a clearly presented, readable description of the treatment of rheumatism. Evidently the author is willing to accept criticism, for now gout is well discussed, desensitization and immunization receive due consideration, each author who is mentioned receives proper bibliographic reference and all literary inelegance seems to have been disciplined. The result is worth while. As was said of each previous edition, in so many different ways, all doctors who deal with arthritic patients will enjoy this book and will find it worth knowing. It summarizes the modern treatment of rheumatism comprehensively and in a particularly readable fashion.

Rural Medicine Edited by G M Mackenzie, M D Price, \$3 50 Pp XVII + 268, with 58 illustrative charts and tables Springfield, Ill Charles C Thomas, Publisher, 1939

This is an interesting book. Members of the staff of the Mary Imogene Bassett Hospital in Cooperstown, N Y, realized that there was but little systematically documented evidence describing what rural medicine amounted to in this country today, what its problems were or, if one knew what they were, how they should best be faced. Therefore, to make a start at finding out more than what was known of such matters, the staff last October organized a conference.

The conference must have been both enjoyable and stimulating. The topics discussed covered a wide range of subject matter. First were considered matters clinical. There were papers on the demography of Otsego County, by Dr J V DePorte, director of the Division of Vital Statistics of the New York State Department of Health, rural hospital morbidity in Otsego County, by Dr E L Crosby, of the department of biostatistics in the School of Hygiene and Public Health at Johns Hopkins University, acute abdominal surgical conditions in a rural hospital, by Dr M A McIver, of Cooperstown, traumatic emergencies in a rural hospital, by Dr J H Powers, Cooperstown, heart disease in a rural community, by Dr F F Harrison, Cooperstown, and vascular disease in a rural community, by Dr David Kydd, Cooperstown.

Next, the health department and school health programs in rural areas were talked over. These topics were introduced by Dr A W Freeman, of Johns Hopkins University, Dr M F Murray, of Cooperstown, and Dr Haven Emerson, of Columbia University.

Postgraduate medical education in rural areas received consideration. In this panel were papers by Dr J D Bruce, of the University of Michigan, and Dr J B Youmans, of Vanderbilt University. Finally, the economics of rural medicine was debated by such authorities as Dr R L Wilbur, of Leland Stanford University, Mr O D Young, of the General Electric Company, Dr V M Hoge, of the Public Health Service, Dr L C Warren, of the Otsego County Medical Society, Dr C C McCoy, of Cooperstown, Dr M M Davis, of New York, and Dr R G Leland, of the American Medical Association.

All the papers which were presented were discussed freely. The book includes the papers read and the discussions which they promoted. There is a bibliography on the general subject of rural medicine, compiled by Dr David Kydd.

Mr Young, in closing the conference, epitomized satisfactorily the usefulness of such a meeting. He said, "It is out of meetings of this kind that interchanges of opinion can be obtained, and progress made so that rigidities melt as between different groups and different individuals." It is pleasant for any one interested to be able to have attended the conference, even vicariously, by studying its record.

Textbook of Medicine By Various Authors Edited by J J Conybeare, M C, D M Odon, F R C P, Physician to Guy's Hospital, London Price, \$6 75 Pp 1112 Fourth edition Baltimore The Williams and Wilkins Company, 1939

This fourth edition of Conybeare's textbook of medicine has had enough revision to keep it well abreast of the times. The chief addition is to the neurologic section, where 100 pages on "psychological medicine" have been added. One questions seriously whether the pages devoted to disorders of the nervous system are not superfluous, not only in this text but in any textbook of medicine intended primarily for medical students. Certainly in most didactic courses in neurology the instructor will prescribe one of the recognized neurologic texts, and the brief material of the medical text, if read at all, will only confuse a subject not too clear in any case. The same may be said of the sections which all texts of medicine contain on diseases of the skin. These chapters seldom exceed a hundred pages and are practically uniformly neglected in the ordinary courses on dermatology. Surely any textbook would not suffer if the three to four hundred pages

devoted to nervous and cutaneous diseases were occupied by an expansion of the general medical material, which has had to be seriously abbreviated to keep the book portable

Conybeare's text is good, however, and there is not enough difference between the nomenclature, materia medica and ideas in this volume and those in ordinary American medical usage to cause difficulty. Curiously, a discussion of sulfamide and sulfapyridine did not get included during the revision, although the use of protamine zinc insulin is taken up and so is the shock treatment of schizophrenia with insulin and metrazol. The reviewer objects, on the grounds that serious confusion may result, to the use of 1 gr. for gr. j, and of 1 grm. for 1 gram (or Gm.). Teaching students dosages is difficult enough when two systems are used, and tragedy will be prevented only when students learn to write and read apothecaries' and metric units in a distinctive manner. One of the functions of a textbook should be to act as a model for the students' actions. This is a minor but not a captious criticism, and the fault is one which can be easily corrected. The text appears to be adequate for its purpose and is remarkably clear and well written. The typography is pleasing because a large, clear type face is used.

Hypertension and Nephritis By Arthur M. Fishberg, M.D. Fourth edition. Price, \$7.50. Pp. 779. Illustrated with 40 engravings and a colored plate. Philadelphia: Lea & Febiger, 1939.

One of the standard monographs used alike by students and graduate physicians is Fishberg's "Hypertension and Nephritis." Of the books devoted to one subject or several related subjects there probably has been no one of its kind that has been more frequently quoted and more generally used, and rightly so. The author has given, in so far as the kidney is concerned, a truly splendid description of renal disease and all its many expressions. In this reference book the inquiring mind may find an excellent account of the pathologic physiology of renal function, and in it may be discovered chapters on azotemia, albuminuria, edema, uremia and tests of renal function which are thoroughly complete. Arterial hypertension in nephritis is most adequately covered. The sections on the nephroses, acute and chronic glomerular nephritis and focal nephritis contain a well rounded description of their clinical and laboratory expressions.

The last few chapters of the book have to do with essential hypertension, its concept, pathogenesis, clinical picture, diagnosis, prognosis and treatment.

It has been five years since the book was last revised. Since that time much has been added to the knowledge of Bright's disease and hypertension. In the preface the author lists a long series of changes that have been made in this edition of his work. Space does not permit recounting these many changes. Suffice it to say that he has incorporated Goldblatt's important contribution on the production of hypertension, a new chapter on azotemia has been added, the surgical treatment of hypertension is discussed in detail, the nature and treatment of the toxemia of pregnancy are presented, and many other important advances have been added.

As with all of the publishers' books, the format of the volume is excellent, there are remarkably few typographic errors and the paper is an excellent grade, so that altogether the book will make a splendid addition to any medical library.

SPONTANEOUS HYPOGLYCEMIA DUE TO ATROPHY OF THE ADRENAL GLANDS

REPORT OF A CASE

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It has been established that hypoglycemia may be due to a variety of causes. In some cases disturbance of the islets of Langerhans, such as hyperplasia,¹ adenoma² or carcinoma,³ has been responsible. In other instances disease of the liver⁴ or insufficiency of the pituitary body⁵ or

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1 Gray, S H, and Feemster, L C. Compensatory Hypertrophy and Hyperplasia of the Islands of Langerhans in the Pancreas of a Child Born of a Diabetic Mother, *Arch Path* **1** 348-355 (March) 1926. Harris, S. Hyperinsulinism A Definite Disease Entity, *J A M A* **101** 1958-1965 (Dec 16) 1933.

2 Whipple, A O, and Frantz, V K. Adenoma of Islet Cells with Hyperinsulinism, *Ann Surg* **101** 1299-1335 (June) 1935. Womack, N A, Gnagi, W B, Jr, and Graham, E A. Adenoma of the Islands of Langerhans with Hypoglycemia. Successful Operative Removal, *J A M A* **97** 831-836 (Sept 19) 1931.

3 Cragg, R W, Power, M H, and Lindem, M C. Carcinoma of the Islands of Langerhans with Hypoglycemia and Hyperinsulinism, *Arch Int Med* **60** 88-99 (July) 1937. Wilder, R M, Allen, F N, Power, M H, and Robertson, H E. Carcinoma of the Islands of the Pancreas. Hyperinsulinism and Hypoglycemia, *J A M A* **89** 348-355 (July 30) 1927.

4 (a) Briggs, J F, and Oerting, H. Extra-Pancreatic Hypoglycemia, *Am J Digest Dis & Nutrition* **3** 436-438 (Aug) 1936. (b) Coller, F A, and Jackson, H C. Surgical Aspects of Hypoglycemia Associated with Damage to the Liver, *J A M A* **112** 128-134 (Jan 14) 1939. (c) Judd, E S, Kepler, E J, and Rynearson, E H. Spontaneous Hypoglycemia. Report of Two Cases Associated with Fatty Metamorphosis of the Liver, *Am J Surg* **24** 345-363 (May) 1934.

5 Foley, M P, Snell, A M, and Craig, W McK. Anterior Pituitary Tumor Associated with Cachexia, Hypoglycemia, and Duodenal Ulcer, *Am J M Sc* **198** 1-8 (July) 1939.

of the adrenal glands⁶ has given rise to severe and at times fatal hypoglycemic attacks. There have been reported numerous other explanations for hypoglycemia, such as lactation, muscular wasting, renal glycosuria, excessive fatigue and fasting.⁷ These conditions only rarely produce severe symptoms. Because cases of severe spontaneous hypoglycemia of extrapancreatic origin are less frequently reported than cases of hypoglycemia due to islet cell changes, it is of interest to report a case in which the hypoglycemia is considered due to insufficiency of the adrenal glands.

REPORT OF CASE

The patient was admitted to the Rochester State Hospital on Feb 7, 1939, with a history of mental trouble for the past seven years. She was 37 years old at the time of admission. The family history was significant in that one brother had committed suicide in a fit of depression and the mother had always been considered "queer" because of her suspicious, domineering manner.

The patient's birth and development were normal. She completed the eighth grade at the age of 15 and is said to have been a bright student. Her menstrual periods began at the age of 14 and were always normal. In 1923, at the age of 22, she was married. There were no pregnancies and no miscarriages or abortions. The past medical history was irrelevant except for "rheumatism" in 1931, which subsided after tonsillectomy in the same year. The patient worked as a stenographer from 1923 until 1932, when she lost her position "because of lack of employment."

In 1932 a change in her personality was noted. She formerly had been an efficient stenographer and had managed her home besides, but she no longer had any interest in her housework and did it very poorly. She began to think that persons were talking about her and spying on her. During the next seven years it was necessary for the family to change residence four times because of the trouble she caused as a result of these ideas. Her paranoid delusions gradually became more prominent, but no striking change was noted until 1938, when she began to have "mean spells." Such spells were of one to two days' duration. During them she would be excited, overactive, irritable and at times violent. Her memory for these spells was good, and she would at times apologize for her behavior. There were no episodes resembling clouded states or convulsions and no periods of unconsciousness. Her husband did not recall that these spells were related to periods of fasting or were relieved by taking food. He admitted that during the past year she had manifested an unusual desire for sweets. During this time her paranoid ideas extended to include her own family and her husband. Strangely enough, she trusted and confided in her mother-in-law. Her mental condition finally necessitated commitment to the Rochester State Hospital.

6 (a) Anderson, I. A., and Lyall, A. Addison's Disease Due to Suprarenal Atrophy with Previous Thyrotoxicosis and Death from Hypoglycemia, *Lancet* **1** 1039-1043 (May 1) 1937. (b) Welty, J. W., and Robertson, H. F. Hypoglycemia in Addison's disease, *Am J M Sc* **192** 760-764 (Dec) 1936. Briggs and Oerting.^{4a}

7 Wauchope, G. M. Critical Review. Hypoglycemia, *Quart J Med* **2** 117-156, 1933.

On admission she was somewhat undernourished and pale. Her height was 5 feet 4 inches (162.5 cm), her weight 114 pounds (51.7 Kg) and her blood pressure 100 mm of mercury systolic and 70 mm diastolic. The results of physical and neurologic examinations were otherwise negative. There was no abnormal pigmentation of the skin or of the buccal mucous membranes. The erythrocyte count was 3,800,000 and the leukocyte count 5,200 in each cubic millimeter of blood, and the value for hemoglobin (Sahli) was 74 per cent. The voided specimens of urine were normal except for a few leukocytes. The Wassermann reaction of the blood was negative.

During the first two weeks in the hospital the patient was seclusive, asocial and negativistic. She expressed many paranoid delusions and had both auditory and visual hallucinations. She often had to be coaxed to eat. A diagnosis of dementia praecox of the paranoid type was made. One day she refused to eat her evening meal because of the belief that it was poisoned. On the following morning she became weak and confused and soon passed into unconsciousness. She was pale and sweaty, and the rectal temperature was 94.6 F. The value for blood sugar was found to be 70 mg and that for blood urea nitrogen 20 mg per hundred cubic centimeters. After approximately thirty minutes she spontaneously

TABLE 1—*Blood Sugar During Dextrose Tolerance Test*

Time	Blood Sugar, Mg per 100 Cc
Fasting	67
½ hour after dextrose	125
1 hour after dextrose	148
2 hours after dextrose	142
3 hours after dextrose	129

recovered consciousness and subsequently took food. On the following day she again refused food and again became confused, weak and stuporous. At that time the value for blood sugar was 66 mg per hundred cubic centimeters. A short time after being forced to drink orange juice, she recovered. During the following week two estimations of the value for blood sugar, made before breakfast, were respectively 80 and 90 mg per hundred cubic centimeters.

One morning she was found cold, pale and sweaty and could not be aroused. The rectal temperature was 94.8 F, the pulse rate 80 per minute, and the pulse was regular. The blood pressure was 80 mm of mercury systolic and 60 mm diastolic. Periodically there was breathing of the Cheyne-Stokes type. Occasional generalized tonic convulsive seizures occurred, lasting one to two minutes. The tendon reflexes were markedly hypoactive, and there was a bilateral Babinski sign. There were wandering movements of the eyes, with a horizontal nystagmus toward the left. At that time the level of blood sugar was 40 mg and that for blood urea nitrogen was 18 mg per hundred cubic centimeters. After intravenous injection of 20 cc of 50 per cent dextrose solution she promptly recovered consciousness.

In an effort to prevent any more serious hypoglycemic episodes the patient was given a high carbohydrate diet, divided into eight small feedings during the twenty-four hours. At this time a roentgenogram of the head was made, which was normal. Three days later a dextrose tolerance test was carried out. After a fourteen hour fast, 50 Gm of dextrose was given by mouth. The values for blood sugar are given in table 1.

An attempt was made to induce an attack by depriving the patient of food. Estimations of the level of blood sugar were made at intervals during a period of forty hours. At the end of that time the patient was stuporous and had to be revived by the intravenous injection of dextrose. The blood sugar levels during this test are given in table 2. During the time this test was in progress, a brom-sulfalein test of hepatic function was made. There was grade 0 retention of dye, indicating normal hepatic function as far as that test was concerned. A few days later an insulin tolerance test was performed. After the patient had fasted for twelve hours, blood was drawn for a sugar estimation, and 47 units of insulin was given intravenously (0.1 unit per kilogram of body weight). The level of blood sugar was ascertained at intervals of fifteen minutes. The results of the test are given in table 3.

These attacks of unconsciousness, therefore, appeared to be definitely associated with periods of hypoglycemia, but except for unusual sensitivity to injected insulin

TABLE 2—*Blood Sugar During Starvation*

Hours After Last Meal	Blood Sugar Mg per 100 Cc
15	71
19	67
23	65
28	52
40	31

TABLE 3—*Results of Insulin Tolerance Test*

Time	Blood Sugar, Mg per 100 Cc	Comment
9 25 a m	90	Given insulin
9 40 a m	62	
9 55 a m	45	Drowsy and complained of hunger
10 00 a m		Crying, restless, sweaty
10 10 a m	34	Flushed, stuporous and restless, given intravenous dextrose and recovered promptly

our investigations had yielded no evidence pointing to any of the extrapancreatic causes which are known to induce a lowering of the level of blood sugar. Therefore an abdominal exploration was carried out by one of us (Stalker) with the hope that a pancreatic tumor might be found and removed. We were unable to find any tumor or abnormality in the entire gland. The small intestine was examined for aberrant pancreatic tissue, but none was found. The liver and gall-bladder were normal. Both kidneys were palpated, and no adrenal tumor could be felt. The question of resecting a portion of the pancreas was seriously considered, but because of the type of patient and her poor general condition it seemed inadvisable. However, in an attempt to bring about, with a minimum of risk, some reduction in secretion and partial atrophy of the gland, the pancreas was transligated at the junction of the proximal one-third and the distal two-thirds. Because of the preexisting anemia, the patient was given a transfusion of 500 cc of blood immediately after the operation.

During the first twenty-four hours after the operation the patient's condition appeared good. The blood pressure stabilized between 90 and 100 mm of mercury systolic and 60 mm diastolic. Estimations of the value for blood sugar were made every four hours, and at the end of twenty-five hours the level was 90 mg per

hundred cubic centimeters. At this time the patient was given an intravenous injection of 1,000 cc of 75 per cent dextrose in physiologic solution of sodium chloride over a period of two and one-half hours. Approximately an hour after completion of the venoclysis, she requested and was given water, which she drank without difficulty. A few minutes later she suddenly became stuporous, with stertorous respirations, and death occurred almost immediately.

Postmortem examination revealed in the pancreas small foci of necrosis in the region of the surgical ligature which had been placed around the pancreas between the head and the body. A white, firm nodule measuring 8 mm in diameter was observed in the substance of the head of the pancreas. No extensive foci of fat necrosis were seen and the operative site was in good condition. After a prolonged and unsuccessful attempt to find the adrenal glands in situ, the tissue overlying the kidneys was removed en masse and dissected. When all possible adipose tissue had been removed from the mass on the right side, a thin, semi-translucent sheet of connective tissue remained, and when this was held up to the

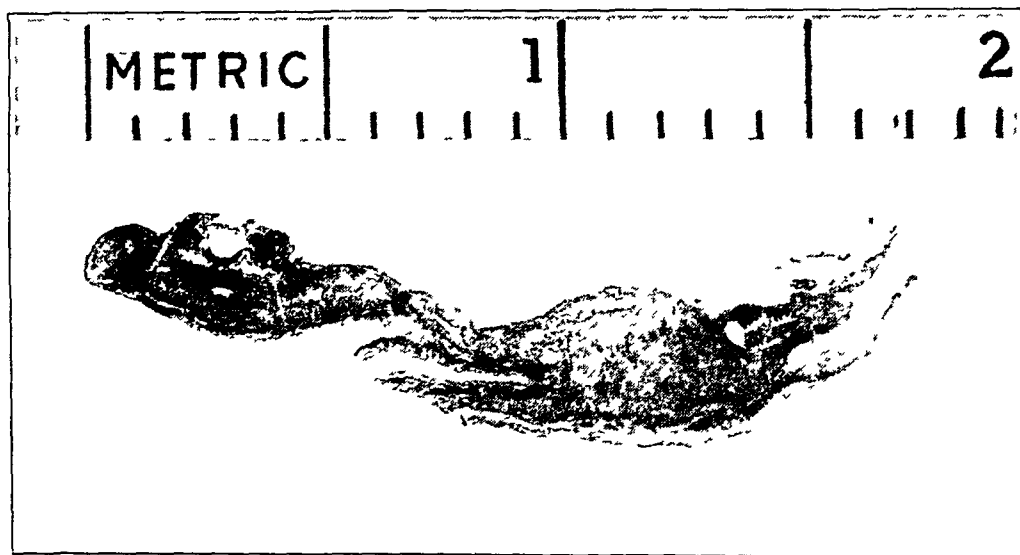


Fig 1—Right adrenal sectioned longitudinally (length, 16 mm), $\times 5$

light a definitely outlined pale brown region could be distinguished. Sections through this region disclosed the fact that the brown tissue was slightly raised above the surface of the sheet of connective tissue, but at no point was it more than 3 mm in thickness (fig 1). A similar procedure with the mass of tissue above the left kidney revealed nothing which could be even tentatively identified as adrenal cortex. The liver was smooth and of normal color and consistency. The ovaries were small and cystic, and the thyroid gland appeared normal in size and shape but was unusually firm when compressed between the fingers. The thymus was almost entirely replaced by adipose tissue. The brain, including the pituitary and pineal bodies, revealed nothing grossly abnormal.

Sections for microscopic examination were taken from all organs, including numerous portions from the suspected adrenal tissue on the right and the mass of tissue above the left kidney. They were fixed in Orth's solution⁸ and stained

8 A mixture of 10 parts of Muller's fluid and 1 part of solution of formaldehyde. Muller's fluid is a weak solution of potassium dichromate and sulfate.

with hematoxylin and eosin. Sections of the liver were frozen and stained with scarlet red.

The most remarkable observation was the state of the adrenal glands. The thin layer of brown tissue on the right proved to be markedly atrophied adrenal cortex with a thin zone of medulla still present (fig 2*a*). A small number of the cortical cells in the zona glomerulosa retained their normal appearance and arrangement, but those of the fascicular and reticular zones were small and irregular, with pale-staining cytoplasm and eccentric nuclei. All the cells had completely lost the foamy appearance that is typically seen when they contain the usual amount of lipoids. The whole picture was one of gradual atrophy without signs of inflammation or replacement fibrosis. The medullary cells were pale

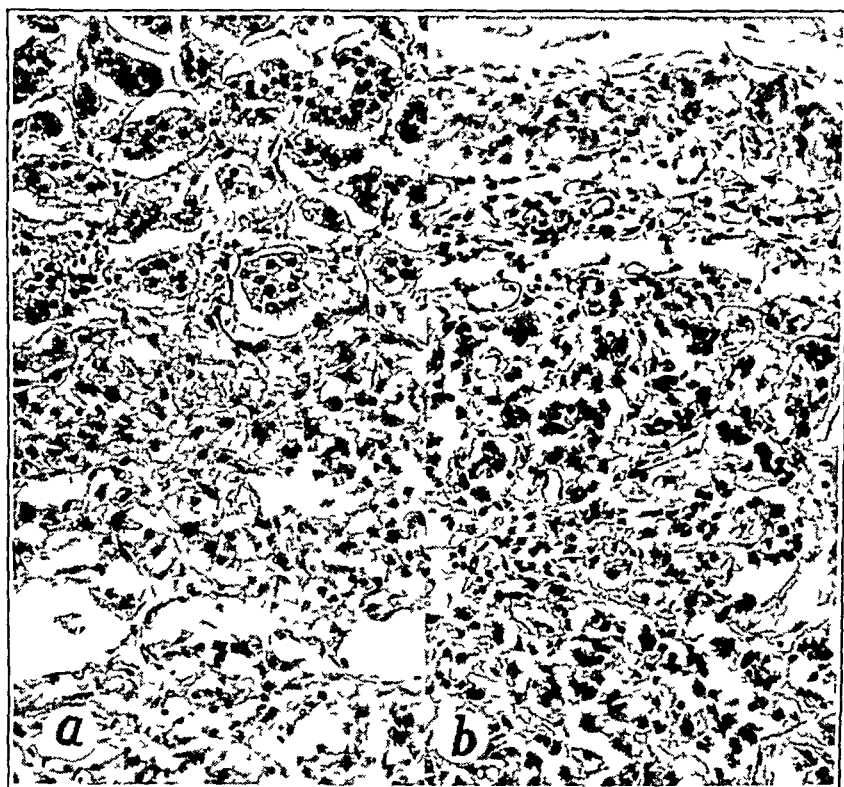


Fig 2—Right adrenal gland (*a*) and left adrenal gland (*b*), showing extreme atrophy of all cells, $\times 145$

and vacuolated, and the chromaffin reaction was negative. Fortunately, one of the blocks cut from the mass of tissue above the left kidney revealed remnants of adrenal cells (fig 2*b*). They were more degenerated than those on the right side, but like them they were not associated with signs of inflammation or foci of necrosis, and only small amounts of fibrous connective tissue were present. Owing to the atrophic condition of these cells it was practically impossible to be certain whether they were cortical or medullary in origin. A rough estimate of the total amount of adrenal parenchyma placed it at 2 per cent of the normal.

Numerous sections taken from various regions of the pancreas revealed nothing particularly abnormal. The islands appeared small, but none of them were degenerated, and there were no large hyperplastic ones. The firm nodule

in the head of the pancreas proved to be merely a mass of fibrous tissue containing a few ducts. Small regions of infarction with fat necrosis were seen surrounding the surgical ligature.

The sections of liver appeared normal, and, although we failed to obtain alcohol-fixed tissue for the glycogen stain, the almost complete absence of the characteristic foamy appearance in the cells made us feel that the amount of glycogen was small. The scarlet red stain revealed only minimal amounts of lipoid in the liver cells.

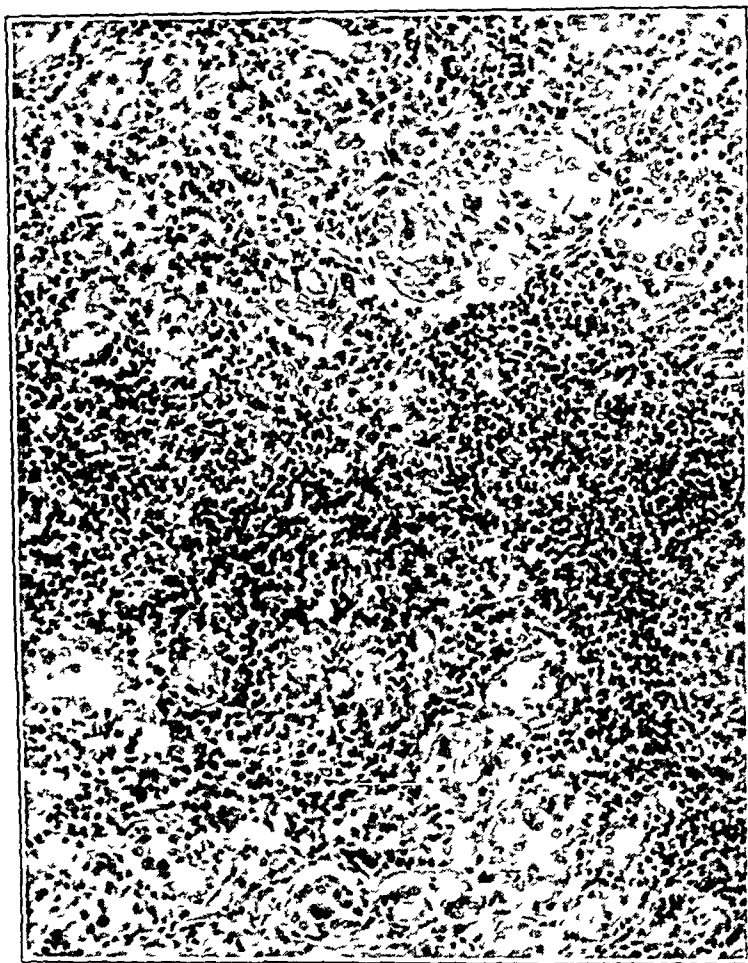


Fig 3—Hashimoto's thyroiditis, $\times 145$

The sections of the thyroid were of interest because they showed that the gross firmness of this gland was due to an extensive and intense degree of inflammation, the so-called Hashimoto's thyroiditis (fig 3). The entire region was made up of enormous numbers of lymphocytes interposed between both hyperplastic and partially degenerated acini. Fibrous tissue was not abundant.

In sections the pituitary gland appeared normal. In the hypothalamus foci of degeneration were observed, similar to those seen by Moersch and Kernohan⁹ in the brains of patients who died in a state of hypoglycemia.

⁹ Moersch, F. P., and Kernohan, J. W. Hypoglycemia. Neurologic and Neuropathologic Studies, *Arch Neurol & Psychiat* **39** 242-257 (Feb.) 1938.

COMMENT

The relation of the adrenal glands to carbohydrate metabolism has been, in recent years, the subject of considerable interest and investigation. Harrop and his co-workers¹⁰ found that in adrenalectomized dogs given cortical extract or salt sufficient to maintain a normal salt and water balance hypoglycemia nevertheless developed if the dogs fasted. Long and Lukens¹¹ found that adrenalectomy ameliorates experimental diabetes in the cat. Himwich and his co-workers¹² showed that ligation of the lumboadrenal veins has a beneficial effect on experimental diabetes in both cats and dogs. The administration of large amounts of adrenal cortical extract tends to restore the diabetes of adrenalectomized-depancreatized animals.¹³ Hypoglycemia is not a common finding in Addison's disease,¹⁴ but in a limited number of cases severe hypoglycemic episodes are an outstanding feature.⁶ In such cases the disturbance of salt and water metabolism may not necessarily parallel the disturbance of carbohydrate metabolism.^{6a} Anderson¹⁵ has reported a case of severe spontaneous hypoglycemia associated with a large carcinoma of one adrenal gland. In summary, we may say that the adrenal glands have an effect on carbohydrate metabolism which is antagonistic to that of insulin. When this effect is removed or sufficiently diminished, hypoglycemia may result.

Our patient had none of the cardinal symptoms of Addison's disease with the possible exceptions of low blood pressure and increased sensitivity to insulin. This is surprising in view of the small amount of adrenal tissue observed at postmortem examination. On two occasions, when the level of blood sugar was abnormally low, that of blood urea

10 Harrop, G. A., Soffer, L. J., Nicholson, W. M., and Strauss, M. Studies on the Suprarenal Cortex. IV. The Effect of Sodium Salts in Sustaining the Suprarenalectomized Dog, *J. Exper. Med.* **61** 839-860 (June) 1935.

11 Long, C. N. H., and Lukens, F. D. W. The Effects of Adrenalectomy and Hypophysectomy upon Experimental Diabetes in the Cat, *J. Exper. Med.* **63** 465-490 (April) 1936.

12 Himwich, H. E., Fazekas, J. F., and Martin, S. J. The Effect of Bilateral Ligation of the Lumbo-Adrenal Veins on the Course of Pancreas Diabetes, *Am. J. Physiol.* **123** 725-731 (Sept.) 1938.

13 Long, C. N. H., Fry, E. G., and Thompson, K. W. The Effect of Adrenalectomy and Adrenal Cortical Hormones upon Pancreatic Diabetes in the Rat, *Am. J. Physiol.* **123** 130-131 (July) 1938. Lukens, F. D. W., and Dohan, F. C. Further Observations on the Relation of the Adrenal Cortex to Experimental Diabetes, *Endocrinology* **22** 51-58 (Jan.) 1938.

14 Kepler, E. J., and Wilder, R. M. Disturbances of Carbohydrate Metabolism Observed in Association with Tumors of the Adrenal Cortex, *Acta med. Scandinav.*, 1938, supp. 90, pp. 87-96.

15 Anderson, H. B. A Tumor of the Adrenal Gland with Fatal Hypoglycemia, *Am. J. M. Sc.* **180** 71-79 (July) 1930.

nitrogen was normal. The acute attacks which this patient suffered were entirely relieved by intravenous injection of small amounts of concentrated dextrose solution. Such treatment would have little or no beneficial effect on an acute crisis of Addison's disease. Nevertheless, we have assumed that adrenal insufficiency was the basic factor in the hypoglycemia. The symptoms manifested by the patient during the terminal crisis were different from those observed in previous attacks, and it is our impression that death was caused by a state of acute adrenal insufficiency. It seems unlikely that hypoglycemia contributed to her death, since the dextrose solution she was given should have been adequate to maintain the blood sugar at a normal level. The postmortem observation of extensive thyroiditis raises the question of whether hypothyroidism played a role in the hypoglycemic attacks. The patient showed none of the usual clinical symptoms of myxedema, and any hypothyroidism she had must have been very mild. As a rule, abnormally low values for blood sugar are not seen in cases of myxedema unless the disease is fairly advanced and even then are usually not accompanied by hypoglycemic symptoms. Therefore, we do not believe that the thyroiditis was of major importance in the development of the hypoglycemic attacks.

We believe that the psychosis in our patient was an independent disease and not a result of the hypoglycemia, even though it is well known that hypoglycemia may produce many types of abnormal mental symptoms¹⁶. However, an outstanding characteristic of these hypoglycemic symptoms is their episodic nature, with periods of normal behavior between attacks. The history of paranoid delusions and seclusive behavior would suggest that a schizophrenic process had been manifest for several years. Her unusual appetite and "mean spells" (which may have been mild hypoglycemic attacks) were of only one year's duration. Furthermore, during the periods when the level of blood sugar was known to have been low, she was somewhat confused and emotionally unstable.

The patient's mental condition precluded our obtaining any information concerning her subjective symptoms either before she came to the hospital or while she was under observation. For that reason, we had to depend on the physical findings and laboratory tests in our attempts to discover the cause of the hypoglycemia. The dextrose tolerance curve,

16 Greenwood, J, Jr. Hypoglycemia as a Cause of Mental Symptoms, *Pennsylvania M J* **39** 12-16 (Oct) 1935. Kepler, E J, and Moersch, F P. The Psychiatric Manifestations of Hypoglycemia, *Am J Psychiat* **94** 89-109 (May 14) 1937. Malamud, N, and Grosh, L C, Jr. Hyperinsulinism and Cerebral Changes. Report of a Case Due to Islet Cell Adenoma of the Pancreas, *Arch Int Med* **61** 579-599 (April) 1938. Wilder, R M. Hyperinsulinism, *Internat Clin* **2** 1-18, 1933.

although abnormal in some respects, was of no material aid. The insulin tolerance test suggested that the patient was hypersensitive to this substance. This might have been interpreted as showing that one or more of the contrainsular factors was deficient but gave no clue as to which factor was at fault.

One of the most remarkable features of this case has been the apparent absence of any typical signs or symptoms of Addison's disease, even though the adrenal glands were almost completely atrophied. Had we but known of this atrophic state, a low sodium and high potassium diet might have aided materially in revealing the association of the hypoglycemia with adrenal insufficiency.

SUMMARY

The case has been described of a young woman suffering from spontaneous attacks of hypoglycemia. At operation, no tumor of the pancreas or any other cause could be found. Postmortem examination revealed extreme atrophy of both adrenal glands and this is considered the cause of the hypoglycemia. Another finding which may possibly have influenced the metabolic disturbances was extensive inflammatory destruction of the thyroid of the type described by Hashimoto.

HYPERTENSION (GOLDBLATT) AND UNILATERAL MALIGNANT NEPHROSCLEROSIS

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AND

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Experimental medicine usually receives its impetus from either clinical medicine or pathology. Thus, by the experimental production of lesions similar to those observed at autopsy, the reproduction of clinical symptoms, thought to be the result of organic changes, is often attempted. More rarely, perhaps, the investigator, without the definite support of clinical or pathologic observations, designs devices which when applied to the laboratory animal produce a definite complex of signs and symptoms. The results so obtained, however, cannot be applied to clinical medicine until a chance patient, dying from the same causes as the experimental animals, shows at postmortem examination conditions similar to those produced experimentally. The correlation with human pathology of results obtained from experimental work must await confirmation until by a "tick of nature" lesions identical to those experimentally produced are seen at postmortem examination.

Goldblatt's¹ experimental production of permanent arterial hypertension by clamping the renal arteries of the dog has found its corollary in human pathology. There are to date a few cases on record in which a "tick of nature" had produced constricting lesions either at the mouth of the renal artery or in the renal artery itself which, as far as could be judged, were responsible for permanent arterial hypertension in the patients. This communication is the result of a study of three patients, in all of whose cases a diagnosis of essential hypertension was made. The autopsy observations on all 3 showed, in the absence of bilateral arteriolonephrosclerosis, constricting lesions of one renal artery or its branches. In 2 of these the rare complication of unilateral malignant nephrosclerosis was found affecting the kidney whose arteries were not constricted. Of special interest is the fact that unilateral malignant nephrosclerosis could not be produced experimentally until recently, and its presence in the human being is, as far

Aided by a grant from the A. B. Kuppenheimer Fund

From the Department of Pathology of the Michael Reese Hospital

1 Goldblatt, H. Experimental Hypertension Induced by Renal Ischemia, in Harvey Lectures Baltimore, Williams & Wilkins Company, 1938, vol 14, p 523

as we could ascertain, an extreme rarity. On the basis of Goldblatt's recent experimental work, malignant nephrosclerosis affecting only one kidney could easily be explained.

REPORT OF CASES

CASE 1—A 46 year old white man, a waiter, complained of pain in the left upper quadrant of the abdomen, of five weeks' duration. He had been perfectly well until seven years previously, when he had symptoms typical of peptic ulcer. Under medical treatment he responded favorably and soon became asymptomatic. Two years later (1933) he sustained fractures of the skull and pelvis. After that time he "just didn't feel well" and complained of vague generalized discomfort. In 1936 he experienced dizziness severe enough to warrant medical attention and was told for the first time that he had "high blood pressure." The dizziness responded to medical care, but the hypertension persisted. A year prior to examination he suffered a fracture of the sternum in an automobile accident. Three months later he complained of dysuria, pain in the left lumbar region and hematuria lasting three days. A physician diagnosed "a passed renal stone." Five weeks before admission to the Michael Reese Hospital he noted pain in the left upper quadrant of the abdomen, which radiated to the epigastrium and to the right upper quadrant. The pain was cutting, constant and relieved by sedatives. There were no associated genitourinary or gastrointestinal symptoms. A loss in weight of 50 pounds (22.7 Kg.) occurred over a period of ten months.

On physical examination the patient appeared chronically ill and pallid. The lungs were clear except for a few rales at the base of the right and impaired resonance at the base of the left. The heart was enlarged, the sounds were of good quality, the rhythm was regular, and a blowing systolic murmur was heard over the entire precordium. The aortic and the pulmonic second sound were both accentuated. The arterial blood pressure in millimeters of mercury was 205 systolic and 140 diastolic. The edge of the liver was 2 fingerbreadths below the costal margin, and the liver was tender. Some tenderness was also elicited in the left upper quadrant of the abdomen, under the costal margin. No abnormal masses were felt in the abdomen. There was a slight tremor of the hands.

Laboratory Data—The erythrocyte count varied between 3,330,000 and 4,840,000 per cubic millimeter. The value for hemoglobin ranged between 50 and 60 per cent, the leukocyte count, between 12,700 and 16,650 per cubic millimeter, with a normal differential count. The value for sugar was 58 mg., and that for non-protein nitrogen ranged between 40 and 84 mg., per hundred cubic centimeters of blood. Repeated examinations of the urine revealed a specific gravity ranging between 1.003 and 1.015, with a 2 plus reaction for albumin and a few leukocytes but no red blood cells. The arterial blood pressure was persistently elevated and varied from 205 to 254 mm. of mercury systolic and 120 to 160 mm. diastolic.

Roentgen study revealed a suggestive mass in the left upper abdominal quadrant, which elevated the left leaf of the diaphragm. In addition, the crater of a duodenal ulcer was noted. An intravenous pyelogram showed no intrinsic changes in the genitourinary tract. The left renal outline was depressed downward. Bilateral ureteral catheterization for study of excretory function disclosed excellent excretion of dye on the left and fair excretion on the right within five minutes after intravenous injection. On retrograde pyelographic examination the left kidney was definitely depressed downward by an extrinsic mass located in the left upper quadrant.

Course—The pain in the left upper quadrant of the abdomen persisted unabated, and the blood pressure maintained a high systolic and diastolic level. Gradually moderate dyspnea and orthopnea and slight edema of the ankles developed. At this time digitalization was started, but signs of moderate congestive heart failure persisted. Ten days before the patient died, he became slightly irrational, muscular twitchings were noted, the respiration was of the Biot type, and a friction rub was heard, localized beneath the lower part of the sternum. The nonprotein nitrogen content of the blood was 74 mg per hundred cubic centimeters, and uremia was diagnosed. The course of the patient's illness during the last two weeks of hospitalization was rapidly downhill. For the three days before death the temperature, which had been normal previously, reached 102 F daily. The clinical diagnosis was uremia, hypertensive cardiovascular renal disease, adrenal tumor and old peptic ulcer.

Postmortem Examination—The more important observations were as follows. The body was emaciated, measuring 160 cm and weighing 60 Kg. Both lower extremities showed a moderate degree of edema. The heart weighed 500 Gm, was enlarged and was displaced to the left. There was recent localized fibrinous pericarditis. The valvular apparatus was intact. The thickness of the left ventricle was 1.8 cm, and that of the right, 0.3 cm. The coronary arteries revealed a moderate degree of intimal thickening but were patent throughout. Both lungs were air containing and reddish brown and on pressure exuded an excessive amount of reddish, frothy fluid. There was no evidence of pneumonia. The liver was somewhat enlarged and was firmer than normal. On section it revealed large and depressed central zones. The spleen was enlarged and firm, the sectioned surface was purplish blue and presented an increase in trabecular markings.

The right kidney was firm and weighed 150 Gm. The capsule stripped with ease to reveal a uniformly and finely granular purplish gray surface speckled with punctate hemorrhagic areas measuring up to 3 mm in diameter. The organ cut with normal resistance. On section the architecture of the cortex was obscured, and many red and gray dots were seen, in addition to minute foci of hemorrhages. The distinction between the cortex and the medulla was not well marked. The pelvis and ureter showed no changes. The right renal artery was widely patent throughout. There was no evidence of arteriosclerosis. The left kidney weighed 150 Gm. It was firmly attached to an overlying cystic retroperitoneal mass which seemed to replace the left adrenal gland. The kidney itself was of normal consistency. Its capsule stripped with ease to disclose a smooth and glistening slate gray surface which showed neither hemorrhages nor granules. In the region of the lower pole there was a yellowish depressed area measuring about 1 cm in greatest dimension, which was sharply defined and which extended in the form of a wedge throughout the cortex. The organ cut with normal resistance, and on section the architecture of the cortex was clearly discernible. The demarcation between the cortex and the medulla was sharp. The pelvis and ureter showed no changes. The left renal artery was distinctly smaller than the right. Its orifice failed to admit a small probe. The vessel was markedly but incompletely obstructed by a firm, grayish, organized, partially calcified thrombus which extended over a distance of 1 cm, starting from a point about 0.2 cm from the orifice of the vessel. Attached to the old thrombus was a more recent, adherent thrombus measuring about 1 cm, which almost completely occluded the lumen of the artery. The three terminal divisions of the left renal artery were widely patent and presented smooth intimal surfaces. The urinary bladder showed multiple single and confluent punctate hemorrhagic spots.



Fig 1 (case 1) —*A*, aorta, renal arteries and kidneys (aorta opened posteriorly) Note the thrombus in the left renal artery, the smooth left kidney, the open right renal artery and the granular surface of the right kidney (About $\frac{1}{3}$ natural size) *B*, thrombus in the left renal artery, note the granularity of the right kidney and the smooth left kidney (0.9 of natural size) *C*, histologic picture of the right kidney Note the necrotic arteriole in about the center of the picture and the surrounding hemorrhage (Iron hematoxylin and eosin preparation, $\times 84$) *D*, section of a glomerulus of the right kidney Note the necrosis of some of the capillaries of the glomerulus (Iron hematoxylin and eosin preparation, $\times 260$)

The right adrenal gland showed no changes. The left adrenal gland was practically replaced by a cystic tumor which on section proved to be an organized hematoma. At the periphery of the hematoma a small, thin rim of yellow adrenal cortical tissue could be recognized. The peripheral portions of the hematoma were completely organized and replaced by connective tissue. The adrenal arteries originated directly from the aorta. A probe inserted into the left adrenal vein opened into the hematoma.

The stomach presented thickened and enlarged rugae. A small stellate scar was noted on the lesser curvature and a similar one in the first third of the duodenum. Throughout the small and large intestines hemorrhagic discolorations were noted, varying from 2 to 3 cm. These were most marked in the cecum. A moderate deposit of fibrin was observed in these regions. The brain was edematous and showed flattened gyri. The entire circle of Willis disclosed moderate arteriosclerosis. Toward the outer portion of the globus pallidum a circumscribed area of hemorrhage was observed, measuring 0.5 by 1 cm. in its greatest dimensions.

Histologic Data—Microscopic examination of the heart disclosed moderate fibrosis, particularly pronounced in the perivascular areas. The pericardium contained some fibrin and a few enmeshed polymorphonuclear leukocytes. The pulmonary alveoli were distended, their septums being frequently ruptured. Large, round mononuclear cells containing golden brown pigment granules were diffusely scattered throughout the alveoli. Sections of the liver revealed marked distention of the central veins and sinusoids with atrophy of the adjacent cords of liver cells. There was a moderate increase in periportal connective tissue. The lumens of numerous arterioles in the sections were distinctly narrowed by thickened and hyalinized walls. There were distended sinusoids in the spleen, and the walls of these were conspicuously thickened. Also, the small arteries and arterioles were markedly thickened and hyalinized.

The outstanding changes in the right kidney (with a widely patent main renal artery) were in the arterioles. Many of the arterioles had completely necrotic walls, the lumens of some of them being occluded by minute thrombi. Here and there arterioles were observed in the midst of a small area of hemorrhage. Often necrotic arterioles with hardly recognizable lumens were seen just entering glomeruli. Occasionally a few polymorphonuclear leukocytes were noted surrounding some of the arterioles. Severe hyalinization with marked constriction of lumens was noted in other arterioles. The glomeruli throughout were more cellular than normal. The capillaries of some of the glomeruli were necrotic, and intra-glomerular hemorrhage was in evidence. Some of the convoluted tubules were dilated and presented granular cytoplasmic changes. Their lumens contained an albuminous precipitate. A number of arteries of the size of interlobular arteries presented marked intimal thickening, with reduplication of their elastic lamellae, and reduction in size of the lumens. In the left kidney (with an obstructed main renal artery) no histologic changes were noted. It must be particularly emphasized that the arterioles showed no changes. (The infarct described grossly was recognized histologically.)

The left adrenal gland showed cortical tissue adjacent to an old, organized hematoma with much hyalinized fibrous connective tissue containing calcific deposits. The arterioles of both glands presented moderate to severe intimal proliferation with hyalinization and narrowing of their lumens. The outstanding change in the pancreas was arteriosclerosis. The submucosal arterioles in the gastrointestinal tract showed moderate to severe intimal proliferation and hyalinization. The brain revealed moderate to severe arteriosclerosis of the smaller arteries and a thrombosed artery in the region of the grossly described recent hemorrhage.

The main pathologic diagnoses were as follows incomplete but marked thrombotic occlusions (old and recent) of the left renal artery, old, small infarct of the left kidney, unilateral malignant nephrosclerosis with arteriolonecrosis (right), localized, fibrinous pericarditis (uremic), hemorrhagic enterocolitis (uremic), edema of the brain (uremic) and recent focal hemorrhage into the right globus pallidum, old hematoma in the left adrenal gland, moderate to severe sclerosis of the arterioles of the spleen, liver, pancreas and intestines, hypertrophy and dilatation of the heart, chronic passive hyperemia of the lungs, liver, spleen and kidneys, edema of the lower extremities, and healed peptic ulcers (gastric and duodenal)

Summary—A 46 year old man who sustained a fracture of the pelvis in an accident six years before death complained of spells of dizziness three years later, at which time arterial hypertension was first diagnosed. A year before death he was in an automobile accident, and three months later a tumor was recognized in the left retroperitoneal space. There was also an old history of peptic ulcer. During hospitalization the patient's blood pressure in millimeters of mercury varied from 205 systolic and 120 diastolic to 254 systolic and 160 diastolic. The non-protein nitrogen content of the blood varied from 40 to 84 mg per hundred cubic centimeters. Congestive heart failure gradually developed, and the patient died of uremia. Autopsy disclosed an organized thrombus in the left renal artery, but the left kidney showed no changes except a small infarct. The right kidney was the seat of arteriosclerosis of the larger arteries and typical malignant nephrosclerosis (arteriolonecrosis). There was also an old, organized hemorrhage in the left adrenal gland. Chronic passive hyperemia was present in the various organs.

CASE 2—A 35 year old woman complained of abdominal distress and vomiting for one month, during which time she had lost 25 pounds (11.3 Kg) in weight. For the last few days diarrhea, with loose watery stools, had been present. Past history revealed that she had had "pyelitis" twelve years previously, severe headaches for over a year and visual disturbances for the past month. On physical examination the patient appeared acutely ill. The rectal temperature ranged between 101 and 102 F. There were marked pallor of the mucous membranes and a peculiar sallow tinge to the skin. The eyelids were puffy. The fundi revealed edema of the papillae, 4 plus. The arteries were practically invisible and apparently spastic. Numerous flame-shaped hemorrhage deposits were noted throughout the retina. The heart was enlarged to the left. There was a rough systolic murmur at the apex. The arterial blood pressure in millimeters of mercury was 224 systolic and 140 diastolic. Laboratory examination showed an erythrocyte count of 2,580,000 per cubic millimeter of blood, with a hemoglobin content of 50 per cent. The leukocyte count was 32,000 per cubic millimeter, with 94 per cent neutrophilic polymorphonuclear leukocytes. The value for blood chlorides was 425 mg per hundred cubic centimeters. The value for nonprotein nitrogen initially was 78 mg per hundred cubic centimeters and subsequently rose to 210 mg. The value for total protein was 6.2 per cent (albumin 4.3, globulin 1.9). The carbon dioxide-combining power was 36.2 volumes per cent. The value for creatinine was 12 mg per hundred cubic centimeters. Examination of the urine

revealed a specific gravity ranging between 1 008 and 1 012 There was albumin (4 plus), and microscopically the urine was loaded with leukocytes, casts of various types and a few red blood corpuscles The stools showed occult blood (4 plus) The patient's course continued progressively downhill She became oliguric, a pericardial friction rub developed, and she died eight days after admission

Postmortem Examination—The more important observations were as follows The body measured 168 cm and weighed approximately 50 Kg The pericardial cavity contained about 300 cc of clear fluid and was partially obliterated by fibrinous adhesions, which were separated with ease The loops of bowel were bound together by thin, fibrinous strands, which could be broken easily The heart was enlarged, weighing 380 Gm, but otherwise showed no changes The lungs, the liver and the spleen showed no changes of note

The right kidney was much smaller than normal, weighing only 30 Gm It was provided with three renal arteries, all of which arose from the aorta and individually supplied the midportion and the upper and lower poles They measured respectively 1, 1.5 and 0.75 mm in diameter The lumen of the vessel supplying the midportion of the kidney was practically occluded by a thick, yellowish intimal plaque located about 5 mm distal to the origin of the vessels The remaining two main arteries were patent The kidney itself was firmly adherent to the perinephric fat tissue and was somewhat firmer than normal Its capsule stripped with ease to reveal a reddish tan, finely and coarsely granular surface with numerous reddish, flat scars of varying sizes On section the cortex was reduced in size, and the line of differentiation between the cortex and the medulla was indistinct The architecture of the cortex was seen more or less clearly, but the medulla in many portions could not be defined The pelvis and calices were dilated The upper calix contained three brownish black, firm, granular stones, measuring up to 1 cm in their greatest diameter The right ureter contained a small amount of yellowish turbid material (pus) The left kidney was slightly enlarged, weighing 160 Gm The organ was somewhat softer than normal, and the capsule stripped with some difficulty to reveal a reddish granular surface speckled with minute and somewhat larger hemorrhagic areas The organ cut with slightly diminished resistance The normal striations of the cortex were everywhere clear, and many reddish and yellowish gray dots and streaks were seen A few minute foci of hemorrhages were noted The pelvis showed no changes The left renal artery was of normal size and showed normal distribution The left ureter contained a small amount of yellowish turbid material (pus) The wall of the urinary bladder was somewhat thicker than normal The mucosa was thrown into folds, and a few hemorrhagic foci were noted

The stomach showed a few hemorrhages in the mucosa but no other gross changes The small and large intestines showed a number of flat ulcerated areas some of which were covered with a pseudomembrane Hemorrhagic foci were observed throughout the mucosa of the small and large intestines, particularly surrounding the ulcerated areas In the region of the ulcers the peritoneal surfaces were covered with fibrin

Histologic Study—The heart muscle was unaltered The pericardial surfaces contained much fibrin and a few enmeshed lymphocytes and polymorphonuclear leukocytes The lungs revealed nothing unusual The central veins and sinusoids of the liver were moderately dilated, and the liver cells throughout had a granular cytoplasm The arterial tree was normal The follicles in the spleen were ill defined, and the pulp showed no changes The arterioles exhibited severe sclerotic changes, but there was no evidence of necrosis

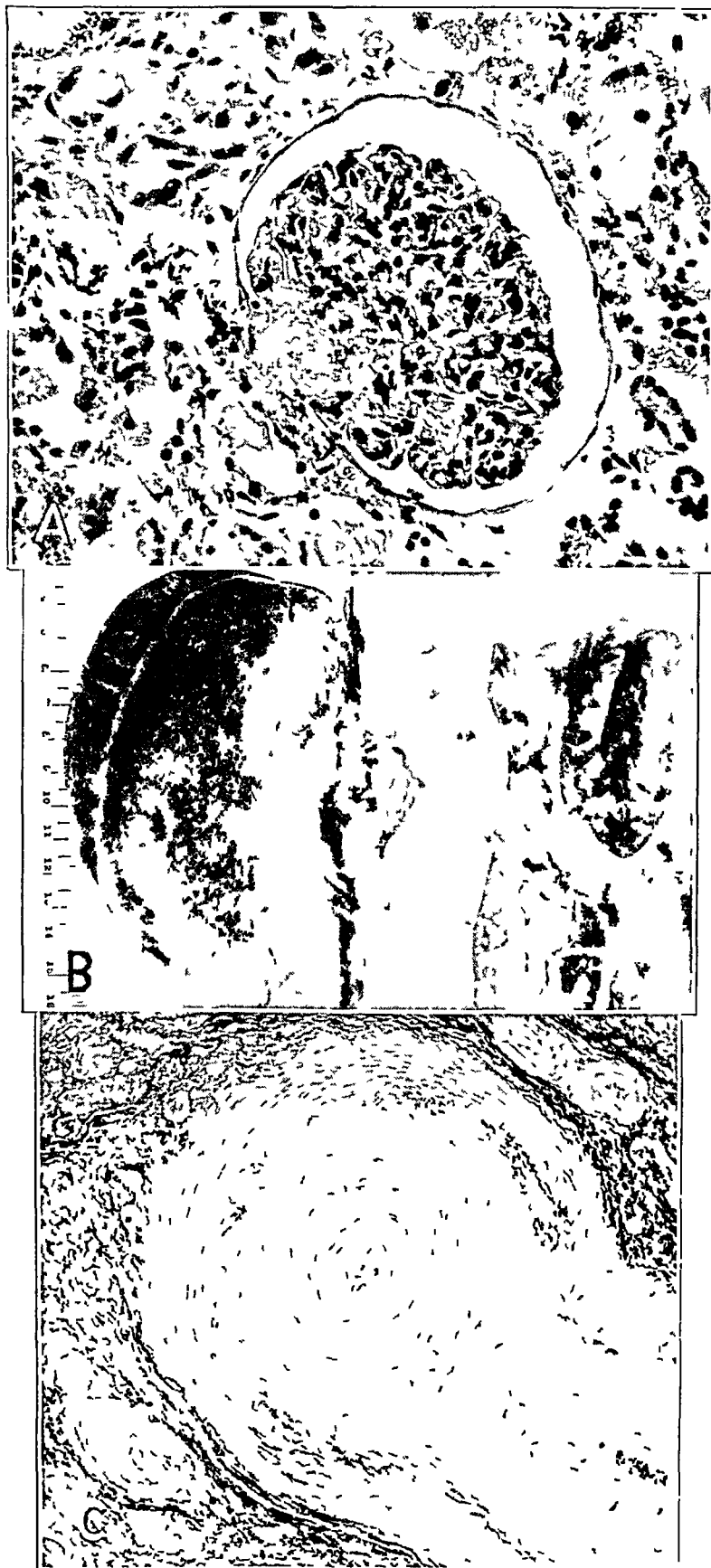


Figure 2

(See legend on opposite page)

Right Kidney (contracted kidney) The glomeruli were irregularly distributed. For the most part, they were completely transformed into fibrotic, hyalinized balls. Several of the normal-appearing glomeruli were encompassed by connective tissue rich in fibroblasts and lymphocytes. Many tubules were dilated, filled with hyaline casts and lined by flattened epithelial cells. Other tubules were small, apparently compressed by markedly increased, dense connective tissue. All large branches of the renal arterial tree presented marked intimal proliferation with hyalinization and severe restriction of their lumens. Many of these vessels revealed only slit-like openings. The arterioles were markedly sclerotic but showed no evidence of necrosis.

The most outstanding changes in the left kidney were observed in the arterioles. Some were severely hyalinized, their lumens practically occluded. The walls of a number of other arterioles were necrotic and their lumens either restricted by thickened walls or occluded by recent hyaline thrombi. Often ghostlike arterioles were seen entering a glomerulus. Occasionally intraglomerular capillaries were also necrotic. Focal hemorrhages and occasional polymorphonuclear leukocytes were noted surrounding several arterioles. In a few glomeruli early fibrotic changes were noted, and the tubules between these glomeruli were atrophic or replaced by connective tissue, which was sparsely infiltrated with lymphocytes. Many glomeruli showed no intrinsic pathologic changes, although occasionally red blood corpuscles were found in their capsular spaces. Some of the tubules were dilated and their lining cells markedly granular. Some tubules contained an amorphous neutrophilic precipitate, others red blood corpuscles and still others a few polymorphonuclear leukocytes. The last-mentioned type of exudate was particularly noted in the collecting tubules. The interstitium showed an excess of dense fibrous connective tissue in which were seen lymphocytes, plasma cells and foci of polymorphonuclear leukocytes. Only slight arteriosclerotic changes were seen in the larger arteries.

There were no histologic changes in the adrenal glands other than a moderate degree of arteriosclerosis of the capsular vessels. Sections taken from the gastrointestinal tract disclosed large foci of necrosis with regions of hemorrhage. Much fibrin with enmeshed polymorphonuclear leukocytes was seen covering denuded regions of the mucosa. In the arterioles of the submucosa a distinct intimal thickening with hyalinization and narrowing of the lumens was noted, but no necrotic arterioles were recognized. The serosa was covered with fibrin and enmeshed polymorphonuclear leukocytes.

The main pathologic diagnoses were unilateral (right) pyelonephritic contracted kidney with nephrolithiasis, multiple renal arteries (three) with severe arteriosclerotic constriction of the lumen of one of them and advanced obliterative intrarenal arteriosclerosis, unilateral (left) recent acute pyelonephritis with superimposed early malignant nephrosclerosis (arteriolonecrosis), hypertrophy of the heart, main part of the left ventricle, acute ulcerative enterocolitis, acute fibrinopurulent peritonitis, and acute fibrinous pericarditis.

Fig 2—*A* (case 1), histologic picture of right kidney. Note the necrotic vas afferens. (Iron hematoxylin and eosin preparation $\times 200$) *B* (case 2) kidneys. Note the small right kidney (pyelonephritic contracted kidney) and the larger left kidney (with malignant nephrosclerosis). *C* (case 2), histologic picture of the right kidney. Note the arteriosclerosis with severe narrowing of the lumen of an intrarenal artery. (Iron hematoxylin and eosin preparation, $\times 56$)

Summary—In a 35 year old woman who had suffered an attack of "pyelitis" twelve years before death marked hypertension gradually developed and she died in uremia. Autopsy disclosed a unilateral pyelonephritic contracted kidney and malignant nephrosclerosis with acute pyelonephritis of the contralateral kidney.

CASE 3—On his first admission to the hospital a 60 year old white man complained of vague gastrointestinal symptoms and headaches. Mental and psychic changes had been noted by relatives during the past year. There was a history of hypertension of about one year's duration. Physical examination revealed peripheral arteriosclerosis, emphysema and a slightly enlarged heart. The arterial blood pressure in millimeters of mercury was 172 systolic and 100 diastolic. Fundoscopic examination disclosed narrowed arteries and "silver-wired" vessels but no hemorrhage or exudate. Laboratory study revealed complete achlorhydria. The urine gave a 1 plus reaction for albumin and ranged in specific gravity from 1.006 to 1.008. The value for nonprotein nitrogen was 33 mg and that for sugar 76 mg per hundred cubic centimeters of blood. The patient remained in the hospital for fourteen days and was discharged unimproved.

The second admission was one month later. The patient had been found in bed, unable to speak, although he attempted to move his lips. Similar transient episodes were reported by the family. In addition, twitchings of his left extremities were noted.

Physical Examination—Cheyne-Stokes respiration was observed. The patient was unable to speak but able to follow instructions. Neurologic examination disclosed rapidly changing signs. The deep reflexes were always present, and the Babinski sign and its confirmatory signs were absent. Rales were heard throughout all lobes of the lungs, but the resonance was normal. The heart showed no abnormalities, the rhythm was regular at 68 beats per minute. The arterial blood pressure was in excess of 260 mm of mercury systolic and 130 mm diastolic. The urine showed no sugar, a 4 plus reaction for acetone and a faint trace of albumin. The patient lapsed into coma and died within eleven hours.

Postmortem Examination—Only the more important observations are given. The body measured 158 cm and weighed about 65 Kg. The right pleural cavity was obliterated by adhesions. The remainder of the serous cavities showed no changes. The heart weighed 400 Gm. The valvular apparatus showed no changes except a moderate degree of arteriosclerosis of the mitral and aortic valves. The myocardium was firm and brownish gray and showed a number of grayish streaks throughout. The left ventricle measured 1.5 cm and the right 0.2 cm in thickness. There were severe sclerosis of the coronary arteries, a moderate degree of arteriosclerosis of the thoracic aorta and severe sclerosis of the abdominal aorta. Both lungs were emphysematous and showed areas of bronchopneumonia. The liver revealed a moderate degree of chronic passive hyperemia.

The right kidney weighed 225 Gm and was larger than normal. Its capsule stripped with ease to reveal a finely and uniformly granular surface. The granules were slate gray and were separated from one another by minute, depressed reddish scars. The organ cut with increased resistance to disclose a well defined cortex and medulla. The cortex was larger than normal, and its striations were clearly recognized. The right pelvis and ureter showed no changes. The right renal artery was widely patent.

The left kidney was much smaller than normal, weighing 50 Gm. It was markedly contracted and densely adherent to the perirenal fat, from which it was

inseparable. A large cyst filled with clear, yellow fluid occupied its upper pole. The capsule stripped with great difficulty and revealed a very irregular granular surface. The granules were separated from one another by a number of scars, some of which were flat and reddish. Others were deep and varied from 2 to 8 mm in their greatest dimension. The organ cut with great difficulty and grittiness. The cortex was reduced in size, and the architecture was obscured. In some portions only a small rim of cortical tissue could be discerned. The pyramids were also reduced in size, and some of them contained calcareous material. The boundary between the cortex and the medulla was indistinct. The renal pelvis was somewhat dilated. The left ureter was thickened, and its lumen was markedly narrowed. Hyalinized and calcified intimal plaques of the aorta in the region of the orifice of the left renal artery produced great constriction of its mouth. The renal artery itself showed thickened and partially calcified walls, but the lumen of the vessel was patent.

There was severe arteriosclerosis of the vessels of the base of the brain. Multiple sections of the brain showed no gross abnormality.

Histologic Study—The outstanding histologic change in the myocardium was a moderate increase in perivascular connective tissue. Only occasionally was focal replacement of muscle fibers by fibrous connective tissue observed. The fibers of the heart muscle seemed larger than normal. There was intimal thickening and narrowing of the lumens of all divisions of the coronary arteries. There was typical, though early, bronchopneumonia. The bronchial lumens were studded with polymorphonuclear leukocytes. Sections of the liver revealed slight dilatation of the central veins and moderate cloudy swelling of the hepatic cells. There was distinct intimal thickening of the arterioles with narrowing of their lumens. Excessive sclerosis and hyalinization with consequent marked narrowing of channels were noted in the arterioles of the spleen.

In the left kidney (with an obstructed main renal artery) only a few normal glomeruli were seen. Many of the glomeruli were hyalinized and apparently drawn together, and the intervening tubules had completely disappeared or were replaced by connective tissue. Some tubules were dilated and filled with a finely granular eosinophilic material or were small and apparently compressed by newly formed connective tissue. There was little cellular infiltration, and only occasional accumulations of lymphocytes were noted. Throughout the section, marked intimal proliferation with consequent severe reduction of the lumens of all the arteries the size of the arcuate arteries was observed, in addition to multiplication of their internal elastic lamellae. There was also marked thickening of the intima of the arterioles. The capillaries throughout were dilated and filled with red blood corpuscles. Here and there small papillary adenomas were seen.

The glomeruli of the right kidney (with a patent main renal artery) were not conspicuously altered. A slight granularity of the cytoplasm of the lining cells of the tubules was noted. Several larger arteries had hyalinized and thickened intima, and the medium and small arteries were only moderately sclerosed, without restriction of the lumens. The arterioles presented distinct but not advanced sclerosis.

Sections of the adrenal glands revealed distinct arteriolosclerosis, particularly pronounced in the capsular region. The brain was the seat of severe arteriosclerosis of all the small vessels, and a number of areas of malacia could be discerned.

The relevant pathologic diagnoses were generalized arteriosclerosis, notably involving the aorta, the left renal artery, the coronary arteries and the cerebral

arteries, severe stenosis of the lumen of the left renal artery, pyelonephritic and arteriosclerotic contractions of the left kidney, compensatory hypertrophy of the right kidney, hypertrophy of the heart, myocardial fibrosis, bronchopneumonia, and encephalomalacia

Summary—A 60 year old patient who had had known hypertension for a year died as a result of bronchopneumonia after he had been the victim of a cerebral accident. Autopsy revealed generalized arteriosclerosis, encephalomalacia, marked arteriosclerotic stenosis of the left renal artery and unilateral severe pyelonephritis and arteriosclerotic contraction of the kidney. The right kidney showed simple compensatory hypertrophy.

COMMENT

These 3 patients are similar in that all had marked arterial hypertension. Two died in uremia and 1 of bronchopneumonia. The autopsy disclosures at first were perplexing because of the contrasting findings in the two kidneys in all 3 instances. From the clinical observation, arteriosclerosis of both kidneys (nephrosclerosis of the arteriolar variety) was expected, as this lesion is often a verification of the diagnosis of essential hypertension. Because of the fact that 2 patients died in uremia, the possibility of superimposed arteriolonecrosis of the kidneys was considered. The first 2 cases are particularly noteworthy, since in both unilateral renal arteriolonecrosis (malignant nephrosclerosis) was encountered.

It would have been extremely difficult, perhaps impossible, to correlate the clinical and pathologic findings in these instances, especially in the first 2, had it not been for the recent investigations pursued by Goldblatt and others, who were able to produce permanent arterial hypertension in the experimental animal. It may be recalled, in short, that in their experiments gradual constriction of both renal arteries of the dog resulted in permanent arterial hypertension. If only one renal artery was constricted, the arterial blood pressure gradually rose, reaching a certain high level, but later returned to the neighborhood of the original basic level. Only in an occasional dog did arterial hypertension persist for months after the renal artery of only one side had been damaged. It was found in these experiments that in animals in which hypertension without accompanying renal excretory insufficiency had existed for several years the arterioles in many structures and organs, except the ischemic kidneys, had thickened walls, owing to hypertrophy of the media. There was no thickening or hyalinization of the intima of these vessels in any organ except the eye. In the retinas of some of the animals, in which significant renal excretory disturbance had not been detected, the arterioles did show signs of sclerosis. In the further pursuit of his work, Goldblatt² found that in those instances

2 Goldblatt, H. Studies on Experimental Hypertension. VII. The Production of the Malignant Phase of Hypertension, *J. Exper. Med.* **67** 809, 1938.

in which constriction of both renal arteries was made very great from the beginning, there resulted arterial hypertension complicated by renal excretory insufficiency and uremia and at autopsy necrosis of the arterioles was observed in many organs (except the kidneys) Goldblatt³ further found that if only one renal artery was clamped and (after development of the arterial hypertension) the ureter of the contralateral kidney was ligated, the dog had uremia Autopsy on these dogs disclosed that the arterioles of many organs and also of the kidney whose artery was unobstructed but whose ureter was ligated showed typical arteriolonecrosis These changes were similar in all respects to those observed in the acute malignant phase of essential hypertension in man (malignant nephrosclerosis) Goldblatt has concluded that in the dog both hypertension and severe disturbance of renal excretory function are necessary for the production of arteriolonecrosis Bilateral sudden excessive constriction of the main renal arteries results in the development of hypertension and uremia and of arteriolonecrosis in many organs, but not in the ischemic kidneys In order to produce this lesion in at least one kidney it is necessary greatly to constrict one main renal artery and to occlude the ureter of the contralateral kidney In the latter, the arteriolonecrosis develops By both methods hypertension and renal excretory insufficiency are produced Since hypertension is not present within the arterioles of the kidney whose artery is constricted, arteriolonecrosis does not develop in this kidney but may be present in other organs and also in the opposite kidney, whose ureter has been ligated but whose circulation is intact so that the vascular tension may be increased in this organ

Knowledge of this experimental work is indispensable for the understanding of the first 2 cases reported in this paper, in both of which there was unilateral malignant nephrosclerosis (arteriolonecrosis) The first instance is particularly interesting because it represents in the human being the exact counterpart of Goldblatt's experiment In the light of these experiments the essentials of the patient's history may be reviewed as follows The patient was well until he sustained a pelvic fracture, after which he "just did not feel well" and subsequently was told for the first time that he had high blood pressure From the observations at autopsy it seems probable that as a result of the accident he sustained an injury not only to the pelvic bones but to the left renal artery Because of the injury to this artery a thrombus gradually formed At autopsy it was observed that the thrombus in parts was very old, calcified and fibrosed The thrombus gradually grew by apposition and led to severe yet incomplete, constriction of the lumen of this artery Thus a process ensued equivalent to Goldblatt's clamping of one main renal artery Whatever caused the rise in arterial

3 Personal communication to the authors

pressure in Goldblatt's experiment caused the rise in arterial pressure in our patient. The thrombus of the renal artery surely could not have completely occluded the artery, or, if it did, there was considerable accessory circulation to the kidney, since on gross and histologic examination it was found to be, in general, normal. Only a small infarct was present, which must be related to the partial thrombosis of the renal artery.

From the foregoing description it is evident that the accident, with the resulting thrombus in the renal artery, was responsible for the gradually developing arterial hypertension. Perhaps at the time of his first accident the patient also had sustained an injury to the left adrenal vein. As a result of the second accident a rupture of the left adrenal vein ensued, leading to hemorrhage into the adrenal gland. This hemorrhage, however, was purely incidental and had nothing to do with the death of the patient. Clinically, however, it played an important role, since the enlarged adrenal gland produced pain, could be palpated and was visible on pyelographic study. The enlarged adrenal gland had been diagnosed as an adrenal tumor.

As a result of the permanent marked arterial hypertension the heart gradually enlarged, and signs of congestive heart failure eventually developed, as was evidenced by the enlarged and painful liver and the swelling of the lower extremities. At that time the nonprotein nitrogen content of the blood began to rise, and the patient soon thereafter showed signs of uremia. The friction rub over the precordium was interpreted as indicating uremic pericarditis. With the onset of congestive heart failure the patient's kidneys apparently could not function properly, and excretory renal insufficiency set in. With the development of the sluggish state associated with congestive heart failure, the renal blood flow diminished steadily and markedly to the point of producing pre-renal azotemia. The ultimate effect of this diminished renal blood flow was exactly the same as that of further mechanical constriction of the renal arteries and impairment of excretory function in the experimental dog. By these circumstances the second factor necessary for production of the malignant phase of hypertension was introduced, namely, renal excretory insufficiency. Autopsy disclosed the arteriolonecrosis and the accompanying acute periarteritis and endarteritis which are characteristic of malignant nephrosclerosis. However, these changes were found in but one kidney, the kidney whose main artery had been patent. These findings are in complete accord with the experimental facts and represent the human counterpart of the animal experiments of Goldblatt. As would be expected, the kidney with the markedly narrowed arterial orifice and lumen failed to show arteriolonecrotic changes, because there existed no hypertension within its vascular tree.

Thus, the relation of cause to effect in this patient is clear. The disease can be traced to the original trauma, which had caused partial thrombosis of the left renal artery. This in turn may be implicated in the gradually developing arterial hypertension. From the foregoing description it is also clear why the patient had the unilateral malignant nephrosclerosis with uremia from which he died.

Case 2 also clearly fulfils Goldblatt's prerequisite for certain instances of hypertension. The patient, a 35 year old woman, having suffered from severe arterial hypertension, died in uremia. Postmortem examination revealed a unilateral pyelonephritic contracted kidney (right) with associated severe obliterative arteriosclerotic changes in the arcuate and interlobar arteries and arteriolosclerosis. Further, one of the anomalous three right main arteries had a frankly constricted lumen. It is evident that the intrarenal arterial changes were produced by the old pyelonephritis which had led to contraction of this kidney. The changes in the renal arterial tree resulted in an ischemic kidney capable of precipitating a hypertensive state. In the presence of the markedly elevated arterial pressure, the arteriolar channels of the left (contralateral) kidney and of other organs and structures eventually showed sclerotic changes. The patient apparently got along quite well in spite of her high blood pressure until early ascending pyelonephritis of the contralateral kidney developed. In view of the severely damaged right kidney, the recent ascending pyelonephritis (left) sufficed to cause excretory renal insufficiency. As in the first case, the two factors essential for the development of unilateral renal arteriolonecrosis were present, namely, arterial hypertension within the vascular system of only one kidney and renal insufficiency. The differences in the 2 cases lie in the agents causing the narrowing of the renal arteries with resulting hypertension and the renal insufficiency. The clinical course and the essential pathologic changes were identical, and both patients died in uremia, just as patients do who present the classic clinical picture of what is called malignant hypertension and who at autopsy show malignant nephrosclerosis.

The intestinal tract of this patient presented grossly the picture of uremic enterocolitis. In experiments on the dog in which, as has been mentioned, constriction of both renal arteries is made severe or in which one renal artery is clamped and the ureter of the other kidney is ligated, there is often found a severe hemorrhagic type of enterocolitis. This is the result of arteriolonecrotic changes of the vessels in the submucosa. In our case such changes in the vessels of the intestinal tract, therefore, were expected. On histologic examination however, few such changes were noted. The enterocolitis was then considered to be of uremic origin.

Since Goldblatt's original experiments there have appeared in the literature reports, notably those by Leiter,⁴ Freeman and Hartley⁵ and Pincoffs and Bradley,⁶ of clearcut examples of constriction of the renal arteries by arteriosclerotic plaques or tumors, with consequent permanent arterial hypertension. The human equivalent, however, of experimentally produced unilateral malignant nephrosclerosis has not, to our knowledge, been recorded. In their study of chronic pyelonephritis, Weiss and Parker⁷ vaguely alluded to unilateral malignant nephrosclerosis, but their pathologic criteria for this condition are unlike the accepted criteria. Very recently, Blackman⁸ reported the occurrence of arteriolonecrotic changes in cases in which hypertension and renal insufficiency coexisted and noted a correlation between these findings and the patency of the main renal arteries. He did not, however, mention the occurrence of such unilateral lesions.

As far as we are able to determine, the occurrence of unilateral malignant nephrosclerosis is an extremely rare finding. It is possible, of course, that if more attention were paid at postmortem examination to the state of both renal arteries and to their mouths and if Goldblatt's experimental results were kept in mind such instances as are reported here would be found more frequently. As it is, perhaps, not so much the stark anatomic findings but his ability to explain the clinical findings in the light of his postmortem observations which intrigues the pathologist, it seems quite likely that more such instances as are recorded here will be made known as soon as the worker in this field is able to interpret the anatomic findings in the light of the history and the course of disease.

The third case is similar to those reported by Butler,⁹ Leadbetter and Burkland,¹⁰ McIntyre,¹¹ and Weiss and Parker.⁷ The patient had

4 Leiter, L. Unusual Hypertensive Renal Disease. 1 Occlusion of Renal Arteries (Goldblatt Hypertension), 2 Anomalies of Urinary Tract, *J A M A* **111** 507 (Aug 6) 1938.

5 Freeman G, and Hartley, G, Jr. Hypertension in a Patient with a Solitary Ischemic Kidney, *J A M A* **111** 1159 (Sept 24) 1938.

6 Pincoffs, M C, and Bradley, J E. The Association of Adenosarcoma of Kidney (Wilms' Tumor) with Arterial Hypertension, *Tr A Am Physicians* **52** 320, 1937.

7 Weiss, S, and Parker, F, Jr. Pyelonephritis. Its Relation to Vascular Lesions and to Arterial Hypertension, *Medicine* **18** 221, 1939.

8 Blackman, S S, Jr. Arteriosclerosis and Partial Obstruction of the Main Renal Arteries in Association with "Essential" Hypertension in Man, *Bull Johns Hopkins Hosp* **65** 353, 1939.

9 Butler, A M. Chronic Pyelonephritis and Arterial Hypertension, *J Clin Investigation* **16** 889, 1937.

10 Leadbetter, W F, and Burkland, C E. Hypertension in Unilateral Renal Disease, *J Urol* **39** 611, 1938.

11 McIntyre, D W. Unilateral Chronic Pyelonephritis with Arterial Hypertension. Apparent Cure After Nephrectomy, *J Urol* **41** 900, 1939.

a unilateral pyelonephritic and arteriosclerotic contracted kidney. The renal artery of this side was markedly constricted by a calcified plaque. The opposite kidney showed moderate arteriosclerosis on microscopic examination but otherwise was practically normal. The patient had had severe arterial hypertension, which probably was the result of the changes in the renal artery and in the intrarenal arteries. The case is included in this series principally for comparison with cases 1 and 2. All 3 patients showed, clinically, arterial hypertension which was the result of constricting lesions in the arterial system of one kidney. The opposite kidneys in cases 1 and 2 showed anatomically the picture of malignant nephrosclerosis (arteriolonecrosis). In the light of the foregoing interpretation this may be easily understood. The question arises now as to why the contralateral kidney of the patient in case 3 did not show arteriolonecrosis. As previously stated, evidence was presented to show that there existed in the patients in cases 1 and 2 excretory renal insufficiency, an essential component for the production of the arteriolonecrosis. It is also noteworthy that these patients died in uremia. It seems evident that the patient in the third case did not live long enough to have excretory renal insufficiency. He died, not in uremia but as a result of bronchopneumonia.

The mechanism for the production of hypertension after constriction of the renal arteries is not known. However, it is apparent that ischemia of the kidney is the essential and constant feature of the phenomenon. Though poorly irrigated with blood, the kidney must contain sufficient functioning tissue if hypertension is to ensue. It is possible that the functioning tissue within the ischemic kidneys elaborates a pressor substance or that the pressor-regulating substances present in the normal kidney are destroyed in the ischemic kidney. Just what is present (or perhaps absent) in an ischemic kidney which is responsible for arterial hypertension is not known.

The question has been raised repeatedly whether Goldblatt's experimental findings are indeed applicable to human pathology and whether they explain the pathogenesis of so-called essential hypertension. As far as these 3 cases are concerned, there can be no doubt that the arterial changes, the counterpart of the clamping of the renal arteries in the experimental animals, were the etiologic factor. Particularly in the first case, in which a thrombus in the renal artery was found, there was, so to speak, an exact imitation by nature of Goldblatt's experiments. Thus, correlation of these experiments with actual human pathology and hypertension in man seems to be definite. In every instance of death from so-called essential hypertension when arterial or arteriolar nephrosclerosis is not observed at autopsy, it is, therefore, imperative to search for a constricting lesion either at the mouth of the renal artery or within the main renal artery. Yet the most common

lesion found at postmortem examination in instances of so-called essential hypertension is arteriolosclerosis of both kidneys (nephrosclerosis of the arteriolar variety). In other words, the equivalent of the clamping of the main renal artery in the experimental dog seems to occur rarely in the human being, but the physiologic equivalent, renal ischemia, is brought about by obliterative sclerosis of the smallest branches, the arterioles. As Goldblatt⁸ has stressed, the arteriolosclerosis of the kidneys corresponds to a million or more minute clamps in each kidney, the corollary of the single clamp around the main renal artery. However, the cause of arteriolosclerosis, which is the apparent cause of so-called essential hypertension, still remains conjectural.

Human beings, in contradistinction to dogs and rabbits, are capable of experiencing a long-standing arterial hypertension after obliterative vascular disease has involved only one kidney. One other experimental animal, the rat, reacts fairly consistently to unilateral renal vascular stenosis, sustained hypertension developing in 65 per cent (Wilson and Byrom¹²). The fact that hypertension may develop in human beings after unilateral renal vascular stenosis brings to realization a very practical point of importance. It means that the internist, when confronted by a patient with persistent arterial hypertension, should keep in mind the possibility that the hypertension may be secondary to renal changes. When this primary and causative disturbance is unilateral and when the effects of the established hypertension on the vascular tree of the rest of the body, particularly the opposite kidney, are still nil or minimal, removal of the unilaterally ischemic kidney may be curative. There are in the literature descriptions of patients with unilateral pyelonephritis and arterial hypertension whom nephrectomy cured of the hypertension (Butler,⁹ Leadbetter and Burkland,¹⁰ McIntyre,¹¹ Boyd and Lewis,¹³ and others). However, it must be especially remembered that nephrectomy for these patients should be considered only in instances of unilateral disease in which the opposite kidney is still free of arteriosclerotic and arteriolosclerotic changes. Failure to adhere strictly to this tenet will result in grave injustice to the patient, for unwarranted removal of the kidney will not cure the hypertension but will immediately make the patient a candidate for the development of fatal uremia incident to the progression of the already present disease process in the one remaining kidney. Such failure of nephrectomy is not a condemnation of the procedure but rather a condemnation of the lack of judgment of the attending internist and surgeon, or of the inability by present methods to detect vascular

12 Wilson, C, and Byrom, F. B. Renal Changes in Malignant Nephrosclerosis. Experimental Evidence, *Lancet* **1** 136, 1939.

13 Boyd, C. H., and Lewis, L. G. Nephrectomy for Arterial Hypertension, *J. Urol.* **39** 627, 1938.

disease in the other kidney Nephrectomy is a perfectly logical and warranted procedure in the very carefully selected case The difficulty in all these instances lies in recognition of the cause of the hypertension and in evaluation of the state of the opposite kidney If the arterial hypertension is caused by bilateral nephrosclerosis of the arteriolar variety, nothing can be done to cure the patient If it is caused by changes in one renal artery or in its intrarenal branches (unilateral pyelonephritis), a timely nephrectomy may cure the patient It will not be difficult for the physician to rule out or to diagnose unilateral pyelonephritis In time it may also be possible to diagnose unilateral ischemic kidney as the result of a lesion at the mouth of the renal artery or within the main renal artery itself Selection of patients for operation must depend on intelligent correlation of the tests of renal function (done separately on each kidney), pyelographic studies and evaluation of the vascular system as determined by the status of its accessible parts (retinal, coronary and peripheral vessels) For the 3 patients described in this communication, nephrectomy at the time of hospitalization, even if possible, would have been unwarranted and harmful, for by that time changes had already taken place in the contralateral kidney and other vessels Much earlier removal of the ischemic kidneys, however, would probably have cured these patients

SUMMARY

Three cases of severe arterial hypertension secondary to unilateral renal vascular stenosis with consequent ischemia of one kidney are reported In 2 of these autopsy revealed unilateral malignant nephrosclerosis (arteriolonecrosis) Because of recent experimental evidence, this unique observation could be readily explained From his experimental studies, primarily concerned with the production of arterial hypertension by clamping the renal arteries in the dog, Goldblatt concluded that both hypertension and renal insufficiency are the minimal prerequisites for the induction of arteriolonecrosis, for in the absence of either of these factors no necrotizing changes are observed The patients in both these cases had severe arterial hypertension brought about by renal artery changes with resulting ischemia of one kidney Both subsequently had renal excretory insufficiency This was precipitated in 1 instance by the onset of congestive heart failure and in the other by the development of acute ascending pyelonephritis in the kidney opposite the ischemic one Because of the presence of the severe arterial hypertension and excretory renal insufficiency, the arterioles in the contralateral kidneys (with a patent vascular system) showed necrotic changes, and these kidneys presented the typical picture of malignant nephrosclerosis The arterioles in the ischemic kidneys revealed no necrotic changes because the stenosis of the renal and

intrarenal arteries militated against the presence of severe hypertension within the arterioles. Thus, the pathogenesis of the malignant nephrosclerosis in these cases is exactly similar to that of the arteriolonecrotic changes produced experimentally by Goldblatt. The third case was included in this report for comparative purposes. This patient died of intercurrent bronchopneumonia and never showed evidences of renal insufficiency. In this instance the requisite factors for development of the malignant phase of hypertension were lacking and, as was expected, there was no evidence of arteriolonecrosis on postmortem examination.

Dr J Gutman and W Buchbinder permitted use of the clinical record in case 1, Dr N Crohn, use of that in case 2, and Dr R Herzog, use of that in case 3.

PULMONARY INFECTION AND NECROSIS IN DIABETES MELLITUS

REPORT OF A CASE OF DISSECTING NECROTIC PNEUMONIA
COMPLICATING PANCREATIC LITHIASIS

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The true nature of the lowered resistance to infection associated with diabetes mellitus is poorly understood despite a wealth of clinical and experimental information. Earlier writers¹ favored the view that it depended on hyperglycemia and saturation of the tissues with dextrose, since many micro-organisms, including diphtheroids, molds and cocci, had been shown to grow by preference in mediums containing sugar. More recent experiments, by Richardson,² Marble and his associates,³ Pillsbury and Kulchar⁴ and others, on the contrary, indicate that increased sugar content of blood and tissues is not significant in bringing about increased growth of bacteria in the body or in diminishing the resistance of the host. Although experimental staphylococcic cutaneous ulcers in dogs undergo rapid necrosis after large intraperitoneal injections of dextrose, this occurs only with solutions sufficiently hypertonic to have toxic effects, and these results can also be duplicated with hypertonic sodium chloride solution⁴.

The humoral mechanism of immunity in diabetic patients has been reported in older studies⁵ to be defective when measured in terms of

From the Laboratory and Medical Service of St Peter's Hospital, New Brunswick, N J

1 (a) Naunyn, B. Der Diabetes Mellitus, in Nothnagel, H. Spezielle Pathologie und Therapie, Vienna, A. Holder, 1900, vol 7, p 170. (b) Lassar, O. Ernährungstherapie bei Hautkrankheiten, Dermat Ztschr **11** 189, 1904.

2 Richardson, R. (a) Immunity in Diabetes. I Influence of Diabetes on the Development of Antibacterial Properties in the Blood, J Clin Investigation **12** 1143 (Nov) 1933, (b) II Relative Importance of Nutritional State and of Blood Sugar Level in Influencing Development of the Agglutinin After Typhoid Vaccine, *ibid* **14** 389 (July) 1935.

3 Marble, A., White, H. J., and Fernald, A. T. The Nature of the Lowered Resistance to Infection in Diabetes Mellitus, J Clin Investigation **17**. 423 (July) 1938.

4 Pillsbury, D. M., and Kulchar, G. V. The Relation of Experimental Skin Infection to Carbohydrate Metabolism. The Effect of Hypertonic Glucose and Sodium Chlorid Solutions Injected Intraperitoneally, Am J M Sc **190**. 169 (Aug) 1935.

(Footnotes continued on next page)

serum complement, bacteriostasis, opsonic index and antibody response to injected antigens. According to more recent observations, however, serum complement⁶ and bacteriostatic and bactericidal properties³ have been shown to be undiminished. Antibody production after injections of vaccine may yield serum titers well within normal limits^{6a}. The explanation of the reduced opsonic activity of diabetic blood has also been shown to lie in a lowered activity of diabetic leukocytes rather than in a fault in serum opsonins^{6a}. The tendency has grown to attach only relative significance to humoral immune responses, since they are now regarded only as special phases or extensions of tissue immunity.⁷

Recent studies⁸ strengthen the view that the lowered resistance to infection observed in persons with diabetes is primarily an aspect of faulty metabolism of the tissues. The evidence at present does not, however, localize the impaired resistance within the cellular elements the activity of which is specifically anti-infective, such as the reticulo-endothelial system,⁹ the lymphatic apparatus and the leukocytes. Instead, the fault apparently resides within all tissues of the body and concerns their intrinsic biologic capacity to withstand injury and intoxication of any kind, whether infectious, chemical or ischemic. Horster,^{6a} for example, demonstrated greater inflammatory reaction and necrosis in skin of depancreatized dogs with diabetes than in nondiabetic controls. This could be accomplished with local injection of turpentine as well as with staphylococci. Shorr observed more rapid in vitro autolysis of

5 Moen, J. K., and Reimann, H. A. Immune Reactions in Diabetes, *Arch Int Med* **51** 789 (May) 1933. Richardson^{2a}

6 (a) Horster, H. Untersuchungen über die durch Krankheiten hervorgerufene Änderung der Disposition für Infektion, bzw. für Erkrankung nach Infektion. Beitrag zur Klärung der Ursache der verminderten Widerstandsfähigkeit des zuckerkranken Organismus gegen Infektion, *Deutsches Arch f klin Med* **176** 502, 1934. (b) Richardson^{2a}

7 Kahn, R. L. *Tissue Immunity*, Springfield, Ill., Charles C. Thomas, Publisher, 1936. Teale, F. H. Some Observations on the Relative Importance of the Reticulo-Endothelial Tissues and the Circulating Antibody in Immunity. I. Bacterial Immunity in Relation to the Role Played by the Circulating Antibody and the Tissues Following Intravenous Introduction of the Bacteria, *J Immunol* **28** 133 (Feb) 1935. II. Hypersensitiveness and Immunity to Foreign Proteins. An Analysis of the Parts Played by the Tissues and Circulating Antibody in These Two States, *ibid* **28** 161 (March) 1935. Dienes, L. The Specific Immunity Response and the Healing of Infectious Diseases, *Arch Path* **21** 357 (March) 1936.

8 Bayne-Jones, S. The Effects of Carbohydrates on Bacterial Growth and Development of Infection, *Bull New York Acad Med* **12** 278 (May) 1936. Horster^{6a}

9 Harrington, H. L., and Huggins, C. Rate of Removal of Thorium Dioxide from the Blood Stream, *Arch Int Med* **63** 445 (March) 1939.

diabetic heart and skeletal muscle than control specimens^{10a} and suggested that the defective oxidation of carbohydrate by diabetic tissue *in vitro* is possibly explained by an inhibitory factor of pituitary origin^{10b} Other possible contributory factors may be mentioned The metabolism of vitamin A is thought to be defective in cases of diabetes,¹¹ as is that of vitamin C¹² Both vitamins are concerned in the maintenance of tissue integrity against infection and other injury The pattern of cell debility in cases of untreated diabetes bears many similarities to that of extreme undernutrition¹³ and avitaminosis¹⁴ as well as of the cachexias associated with advanced malignant disease, heart failure and senility

The pernicious nature of infection in cases of diabetes is a matter of everyday experience to the clinician, not only in respect to the skin and the contiguous mucosae but in respect to the viscera, particularly the lungs The threat of pulmonary tuberculosis has received recent emphasis by Fitz,¹⁵ Root,¹⁶ Steinbach and his associates,¹⁷ McKean and Myers¹⁸ and many other writers Both "diabetic phthisis" and "diabetic nonputrid gangrene of the lung" with characteristic extensive necrosis of lung tissue are mentioned frequently in the older (preinsulin) literature of diabetes¹⁹ For the former are described enormous numbers

10 Shorr, E (a) Personal communication to the author, (b) Restoration of Carbohydrate Oxidation in Diabetic Tissue *in Vitro*, *Science* **85** 456 (May 7) 1937

11 Ralli, E P, Pariente, A C, Brandaleone, H, and Davidson, S Effect of Carotene and Vitamin A on Patients with Diabetes Mellitus III Effect of Daily Administration of Carotene on Blood Carotene of Normal and Diabetic Individuals, *J A M A* **106** 1975 (June 6) 1936

12 Pfleger, R, and Scholl, F Diabetes und Vitamin C, *Wien Arch f inn Med* **31** 219, 1937

13 Bieling, R Unterernahrung und Infektion, *Deutsche med Wchnschr* **53** 228 (Feb 4) 1927

14 Clausen, S W The Influence of Nutrition upon Resistance to Infection, *Physiol Rev* **14** 309 (July) 1934 Robertson, E C The Vitamins and Resistance to Infection, *Medicine* **13** 123 (May) 1934

15 Fitz, R The Problem of Pulmonary Tuberculosis in Patients with Diabetes, *Am J M Sc* **180** 192 (Aug) 1930

16 Root, H F (a) Association of Diabetes and Tuberculosis, *New England J Med* **210** 1 (Jan 4), 78 (Jan 11), 127 (Jan 18), 192 (Jan 25) 1934, (b) Tuberculosis Complicating Diabetes, in Joslin, E P The Treatment of Diabetes Mellitus, ed 6, Philadelphia, Lea & Febiger, 1937, chap 21, p 496

17 Steinbach, M M, Klein, S J, and Deskowitz, M Experimental Diabetes and Tuberculosis in the Dog, *Am Rev Tuberc* **32** 665 (Dec) 1935

18 McKean, R M, and Myers, G B Metabolic Aspect of Associated Diabetes Mellitus and Pulmonary Tuberculosis, *Ann Int Med* **8** 1591 (June) 1935 Myers, G B, and McKean, R M Diabetes and Tuberculosis, *Am Rev Tuberc* **32** 651 (Dec) 1935

19 (a) Kornrumpf, P Ueber Lungenkomplaktionen bei Diabetes, Inaugural Dissertation, Berlin, E Ebering, 1914 (b) Fink, H Beitrag zur Lehre von

of tubercle bacilli, for the latter, a mixture of large numbers of molds, diphtheroids and other saprophytes. Tuberculosis in an untreated diabetic person may, under certain conditions, bring about rapid liquefying necrosis of almost an entire pulmonary lobe. At autopsy only a shell of thickened pleura remains, enclosing a giant cavity filled with sloughed tissues.²⁰ Proper treatment, however, promises the diabetic person with pulmonary tuberculosis a far more hopeful outlook.²¹

The predisposition of the inflamed lung in cases of untreated diabetes to undergo necrosis may be apparent even in the presence of common grippal bronchitis and bronchopneumonia^{10a} and to an even more striking degree in cases of fungous infections²² and of putrid abscess of the lung.²³ Although a low incidence of pneumococcic lobar pneumonia is recorded in association with diabetes,²⁴ cases of severe pulmonary infection have been described in which the early course resembled lobar pneumonia clinically but in which the outcome was atypical if not disastrous. This will be discussed later.

Especial attention should be given to the role played in pulmonary infection by deficiency of the pancreas when it is caused by chronic disease of the parenchyma with extensive atrophy. In such a case fatty diarrhea goes hand in hand with diabetes mellitus to bring about pronounced emaciation and physical debility. Despite the fact that diabetes is often mild, a high incidence of pulmonary infection is reported. Among the best known instances are those which occur in cases of congenital steatorrhea with fibrosis of the pancreas.²⁵ Death occurs usually in early childhood as a result of bronchopneumonia. Postmortem

der diabetischen Lungenerkrankung, Inaug. Dissert., Giessen, C. von Munchow, 1887. (c) Marchand, F. Ueber den Ausgang der Pneumonie in Induration, Virchows Arch f. path. Anat. **82** 334, 1880. (d) Fraenkel, A. Spezielle Pathologie und Therapie der Lungenkrankheiten, Berlin, Urban & Schwarzenberg, 1904. (e) Naunyn,^{1a} pp. 218 and 220.

20 Moolten, S. E. Unpublished data.

21 Wessler, H., and Hennell, H. Benign Pulmonary Tuberculosis with Diabetes, Am. Rev. Tuberc. **27** 47 (Jan.) 1933. Root^{16b}.

22 Furbringer, P. Beobachtungen über Lungenmycose beim Menschen, Virchows Arch f. path. Anat. **66** 330, 1876. Watjen, J. Durch Schimmel- und Sprosspilze bedingte Erkrankungen der Lunge, in Henke, F., and Lubarsch, O. Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1931, vol. 3, pt. 3, p. 481.

23 Rabin, C. B. Personal communication to the author.

24 Marble, A., in Joslin, E. P. The Treatment of Diabetes Mellitus, ed. 6, Philadelphia, Lea & Febiger, 1937, chap. 14, p. 407. Root^{16b}.

25 (a) Harper, M. H. Congenital Steatorrhea Due to Pancreatic Defect, Arch. Dis. Childhood **13** 45 (March) 1938. (b) Parmelee, A. H. The Pathology of Steatorrhea, Am. J. Dis. Child. **50** 1418 (Dec.) 1935. (c) Andersen, D. H. Cystic Fibrosis of the Pancreas and Its Relation to Celiac Disease, *ibid.* **56** 344 (Aug.) 1938.

examination reveals subacute bronchopneumonia with purulent bronchitis, widely disseminated miliary abscesses and bronchiectases. Since steatorrhea is often associated with deficient absorption of fat-soluble vitamins, these pulmonary lesions have been attributed to changes brought about by vitamin A deficiency.²⁶ In Andersen's series of 49 cases, keratinizing metaplasia of the bronchial epithelium was frequently noted.^{25c} In this connection it is important to recall the fact that xerophthalmia occurs only in extreme cases of vitamin A deficiency in the human being, while fairly early in the course of the deficiency the ciliated epithelium of the respiratory tract may disappear.²⁷

Severe pancreatic deficiency of long duration in the adult is best exemplified in pancreatic lithiasis. The literature of this condition is rich in instances of its association with pulmonary tuberculosis of great destructiveness.²⁸ The high incidence of this association led, in fact, to the erroneous supposition of early observers that the pancreatic lesion is a result of tuberculosis.^{28b}

Aside from tuberculosis, no well defined type of pulmonary disease has been described in any of the reported cases of pancreatic calculus except one. This was a case published in the Dutch literature by Peutz²⁹ in 1930 under the descriptive title of "acute aputrid necrosis of the lung." The patient was a diabetic man aged 43. He had been treated for diabetes since the age of 25 and had recently become considerably emaciated. Four weeks before entering the hospital he had a productive cough and dyspnea and felt sudden severe pain in the right side of his chest. On admission he was cyanotic and intensely dyspneic and had physical signs suggestive of pneumothorax. The roentgenogram was reported to show encapsulated hydropneumothorax. Autopsy revealed large, irregular intrapulmonic cavities with a shaggy lining of recently softened lung tissue. They were filled with nonputrid liquid pus and air and occupied most of the right lung and a few areas of the left. One of the cavities in the lower lobe of the right lung was the size of a fist. The surrounding lung was consolidated and had patches of peculiar yellowish white necrosis which had not yet undergone softening. There were no evidences of tuberculosis grossly or microscopically. The pan-

26 Darrow, D. C., in discussion on Parmelee.^{25b} Andersen.^{25c}

27 Wolbach, S. B., and Howe, P. R. Epithelial Repair in Recovery from Vitamin A Deficiency, *J. Exper. Med.* **57** 511 (March) 1933.

28 (a) Mockel, E. Ueber Lithiasis pancreatica mit vier eigenen Fallen, *Frankfurt Ztschr. f. Path.* **24** 78, 1921. (b) Gruber, G. B. Speicheldickung und Speichelsteine im Pankreas, in Henke, F., and Lubarsch, O. *Handbuch der speziellen pathologischen Anatomie und Histologie*, Berlin, Julius Springer, 1929, vol. 5, pt. 2, p. 382. (c) Ackman, F. D., and Ross, A. Pancreatic Lithiasis, *Surg., Gynec. & Obst.* **55** 90 (July) 1932.

29 Peutz, J. L. A. Acute aputriede longnecrose bij pancreasdiabetes, *Nederl. tijdschr. v. geneesk.* **74** 3659 (July 19) 1930.

creas was almost entirely transformed into dense scar tissue and contained many small calculi

A close counterpart of this case is seen in the following case

REPORT OF CASE

J J, a man aged 54, entered St Peter's Hospital with "advanced pulmonary tuberculosis and diabetes mellitus" For five years he had been subject to attacks of agonizing cramplike pain in the epigastrium, at times the attacks persisted as long as five days despite repeated large doses of morphine During the later months of his illness he had persistent diarrhea and began to lose weight rapidly Diabetes was discovered and treated by diet without insulin Three months before admission to the hospital he began to cough and expectorate frequently On admission he was gravely ill and was emaciated to a striking degree His feet were edematous Marked dulness and numerous moist rales were detected over the entire right lung His urine contained 5 per cent sugar but no acetone, the value for blood sugar was 333 mg per hundred cubic centimeters The level of hemoglobin was normal (85 per cent, Dare), there were 4,700,000 red blood cells and 7,250 white blood cells per cubic millimeter, with 80 per cent polymorphonuclear leukocytes The temperature ranged between 97 and 99.4 F He died thirty-six hours after admission

Postmortem Examination—The subject appeared extremely cachectic and emaciated The right lung was heavy and largely consolidated The upper lobe was partly adherent, and its visceral pleura was greatly thickened by fibrosis On section the entire upper lobe exhibited grayish white consolidation with numerous large areas of partial or complete liquefaction necrosis Many sequestrums of inflamed and necrotic lung tissue floated partly free in the cavities thus formed, and some of the parenchyma had become dissected away from the surrounding inflamed tissue as well as from the pleura and interlobular septums and bronchi Fresh cavities had shaggy, friable walls, older ones were lined in part by smooth whitish material like pyogenic membrane They contained grayish muddy fluid without distinctive odor In certain portions of the consolidated areas small foci of tuberculosis were also seen, which were recognized by their dense fibrous scar tissue containing anthracotic pigment and both calcified and caseous deposits The blood vessels showed no significant changes

Microscopically many shreds of faintly stained necrotic parenchyma were seen These were composed of the ghosts of alveolar septums containing necrotic exudate and ghosts of occasional bronchi and blood vessels (fig 1) A wide zone of suppuration separated these necrotic areas from the remaining tissue and formed the lining of cavities (fig 2) In some areas tissue necrosis had just begun, and only an indefinite line of demarcation had appeared at the edges The intervening parenchyma exhibited exudation varying from edema and epithelial desquamation to massive infiltration with polymorphonuclear leukocytes and fibrin, especially in the vicinity of the most active necrosis Patchy carnification was also noted The bronchi and bronchioles in intact areas were distended with partly necrotic purulent exudate The blood vessels in necrotic areas were completely destroyed In the line of demarcation they exhibited inflammatory thromboses, the thin-walled veins being chiefly affected There were no vascular lesions, either arterial or venous, in areas proximal to the demarcating inflammation

The tuberculous foci were also affected by necrosis, in a few the envelope of scar tissue had been destroyed and the caseous contents partly liberated Small

secondary patches of recent tuberculosis were noted in close proximity to the necrotic areas described and often merged insensibly into them. These exhibited caseation with very little formation of granulation tissue. Giant cells of the Langhans type were lacking.

Bacterial stains of the necrotic portions revealed enormous numbers of bacteria and bacterial colonies, chiefly gram-positive bacilli morphologically suggestive of *Bacillus subtilis* and very short gram-negative bacilli. Prolonged search

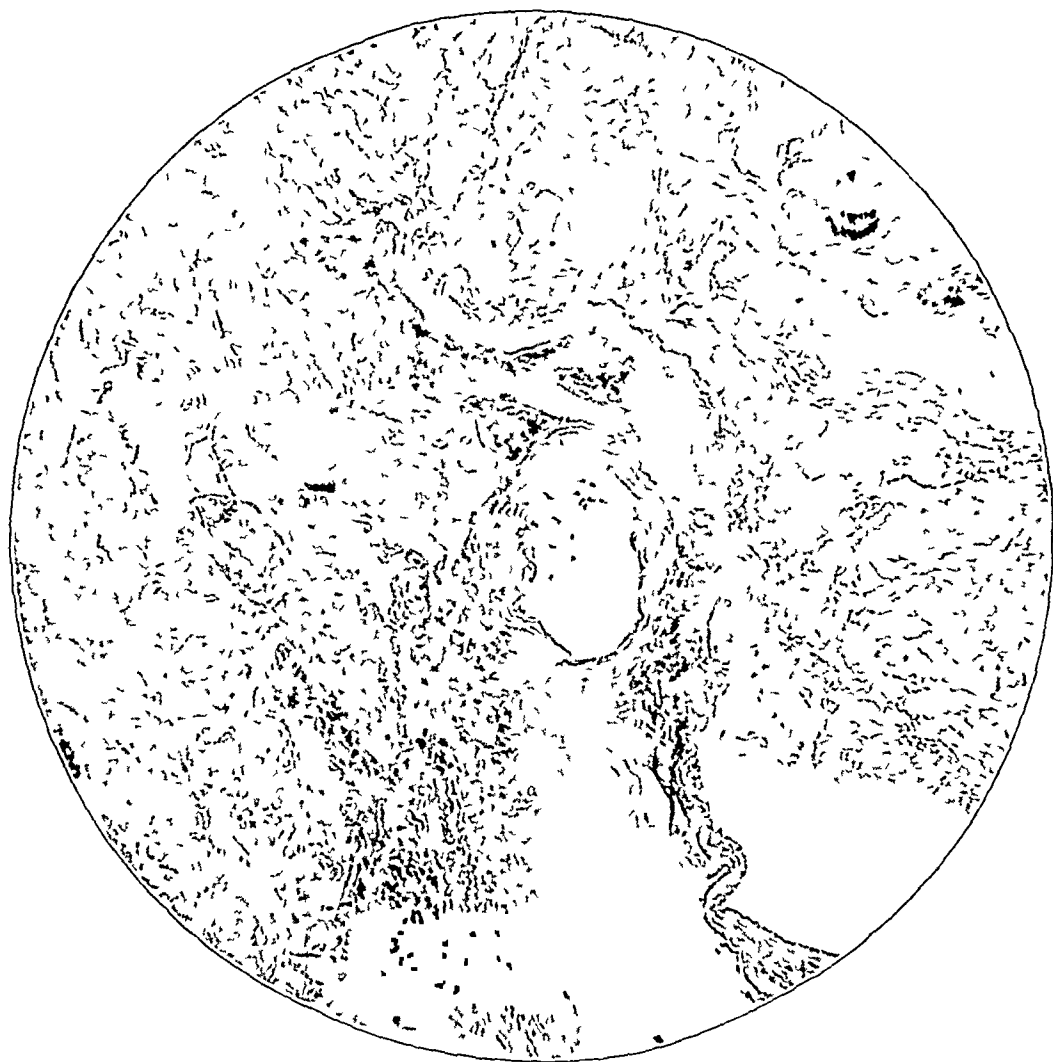


Fig 1—Sequestrum of the lung, alveolar and bronchial "ghosts" containing faintly stained exudate of fibrin and leukocytes are seen

yielded no evidence of yeasts, molds or encapsulated bacilli or cocci. Tubercle bacilli were not seen in these necrotic areas. A few were discovered in the tuberculous foci just described.

The lower lobe of the right lung was markedly congested and presented a few small scattered areas of recent caseous tuberculosis. These presented almost no granulation tissue reaction but contained many tubercle bacilli. The left lung showed only congestion and some emphysema.

The pancreas was of average size (fig 3) but exceedingly hard and buried in adhesions. It was cut with great difficulty and seemed to be completely transformed into fibrous tissue of almost woody consistency. Within it were embedded

many white calcareous particles. The main pancreatic duct (Wirsung's) was greatly dilated throughout its length. A white calculus 4 by 4 by 7 mm was firmly impacted in its lumen, about 1 cm above its duodenal orifice. Several



Fig 2—Wall of the cavity, showing the pyogenic membrane and separation of a sequestrum of necrotic lung tissue

smaller, irregular, gritty white calculi lay free in the lumen behind this. Microscopically all but a few scattered nests of gland tissue had become replaced by dense hyaline scar. Within these remnants the acini were loosely disposed, in some areas they were fairly well preserved and elsewhere they were atrophic (fig 4)

The collecting ducts were dilated and filled with epithelial debris, a few leukocytes and rounded laminated masses resembling corpora amylacea. The islets of Langerhans were few and somewhat atrophic, with small round pyknotic nuclei.

Both kidneys were studded with innumerable tiny furuncular lesions which projected slightly on the surface and on cut section extended toward the medulla as tapering whitish streaks. Microscopically they appeared as minute abscesses containing a mixture of bacteria morphologically similar to those seen in the sections of the necroses within the lung. Diffuse infiltration of polymorphonuclear leukocytes extended irregularly through the remainder of the interstitia.

The colon was moderately distended with pasty, unformed brownish gray feces. When held to the light the feces had a conspicuous silvery sheen, as though there were a high fat content. The odor was distinctively rancid.

The myocardium, liver and kidneys presented parenchymal degeneration, such as is seen in acute infection. Microscopically the liver cells were somewhat shrunken and were devoid of fat vacuoles, occasional nuclei contained glycogen vacuoles. The portal fields showed moderate infiltration of lymphocytes and increase in fibrous tissue. The myocardial fibers stained unevenly, often with hydropic replacement of fibrillae or vacuoles and with much bipolar yellow pigment.

The spleen presented the changes of severe infection. Both adrenals were enlarged considerably by rounded, bulging acorn-sized tumors composed of yellowish tissue, histologically they were composed of hyperplastic cortex containing abundant lipid and presenting a few areas of recent focal degeneration.

Clinical Diagnosis—The clinical diagnosis was diabetes mellitus without ketosis.

Anatomic Diagnoses—The anatomic diagnoses were as follows: multiple calculi of the pancreatic duct, with atrophy and fibrosis of the entire pancreas, steatorrhea, extreme emaciation and cachexia, anasarca, massive necrotic pneumonia of the upper lobe of the right lung, with multiple cavities (pneumonia dissecans necrotica), slight localized recent tuberculosis of the upper and lower lobes of the right lung, secondary to decapsulation of old fibrocaceous tuberculous foci of the upper lobe, conglomerate miliary hematogenous ("excretion") abscesses of both kidneys with acute interstitial nephritis, and adenomatous hyperplasia of the cortex of the adrenal glands with focal degeneration.

Comment—Excellent discussions of pancreatic calculus are available in the writings of Gruber,^{28b} Gross,³⁰ Mayo Robson and Cammidge,³¹ Barron³² and Crohn.³³ Attacks of severe epigastric pain, prolonged fatty diarrhea, diabetes mellitus and extreme emaciation constitute a fairly typical clinical syndrome, permitting easy recognition in the advanced stages of the disease. Diagnosis before the development of

30 Gross, O. Konkremete im Pankreas, in Gross, O., and Guleke, H. Die Erkrankungen des Pankreas, Enzyklopaedie der klinischen Medizin, Spezieller Teil 5 c, Berlin, Julius Springer, 1924, p. 206.

31 Mayo Robson, A. W., and Cammidge, P. J. The Pancreas. Its Surgery and Pathology, Philadelphia, W. B. Saunders Company, 1907.

32 Barron, M. The Relation of the Islets of Langerhans to Diabetes with Special Reference to Cases of Pancreatic Lithiasis, Surg., Gynec. & Obst. **31** 437 (Nov.) 1920.

33 Crohn, B. B. Disturbances of Metabolism Accompanying Pancreatic Disease, in Barker, L. F., and others. Endocrinology and Metabolism, New York, D. Appleton and Company, 1922, vol. 4, p. 657.

irreversible pancreatic insufficiency, however, is much more difficult without roentgen examination. Fortunately, practically all pancreatic stones are radiopaque and thus permit early diagnosis and the possibility of surgical cure.³⁴

NECROSIS OF THE LUNG AND NECROTIC PNEUMONIAS

Interest in the present case centers principally on the pulmonary lesion, the outstanding feature of which was necrosis. While necrosis in general is not uncommon in a variety of pulmonary diseases, its significance is almost always bound up with the nature of the underlying

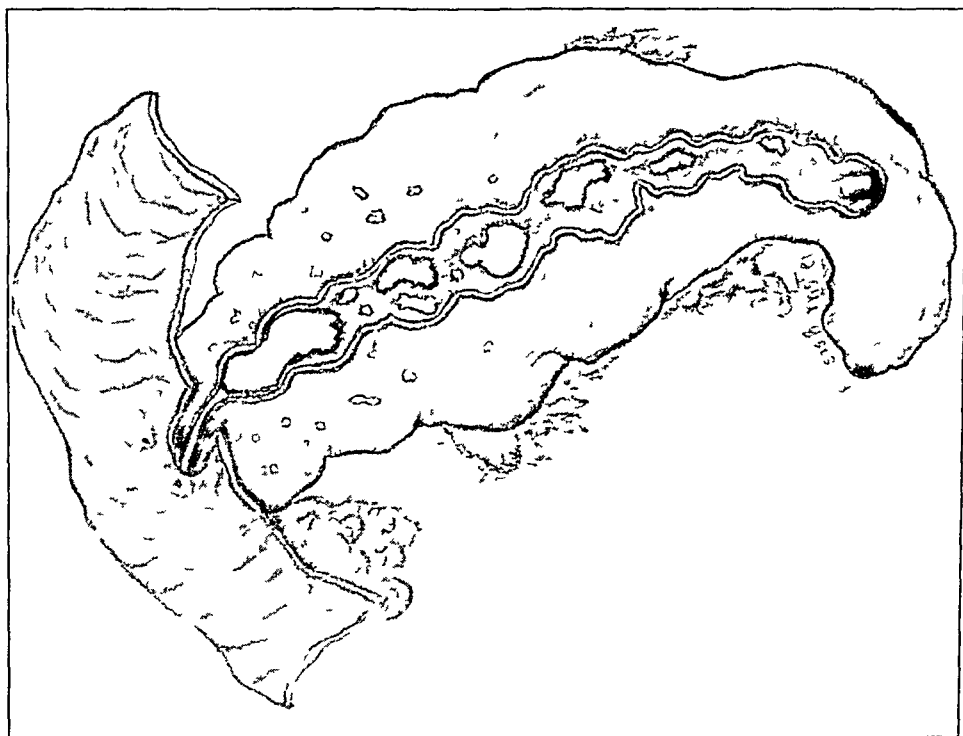


Fig 3—Multiple calculi of the main pancreatic duct and of the smaller ducts. Note the marked fibrosis of the entire gland and the separate opening of the pancreatic duct into the duodenum 1 cm. from the papilla of Vater.

infection. Minute areas of necrosis are fairly common in ordinary bronchopneumonia but are not detectable clinically. They are apparent at autopsy as small grayish white areas within larger patches of severe inflammation.³⁵ This may be marked in influenzal bronchopneumonia.^{35b} In the earliest stages of necrosis the affected tissue is slightly firmer than normal, suggesting a process of coagulation, and owes its grayish white color to bloodlessness brought about by injury to its capillaries. The framework of elastic tissue is often well preserved, as is proved by

34 Lindsay, E. C. A Further Case of Multiple Pancreatic Calculi. Removal and Recovery, *Lancet* 1:700 (April 7) 1928. Bost, T. C. Pancreatic Lithiasis

histologic methods, but the other elements of the parenchyma, as well as the cellular and fibrinous exudates, stain poorly or not at all. When softening occurs, fragments of necrotic parenchyma may still be recognized as "ghosts" within areas of suppuration.

It has been suggested³⁶ that such foci of necrosis within the parenchyma of the lung are the basic factor in the formation of the common saccular bronchiectases. According to this theory, as air is sucked into

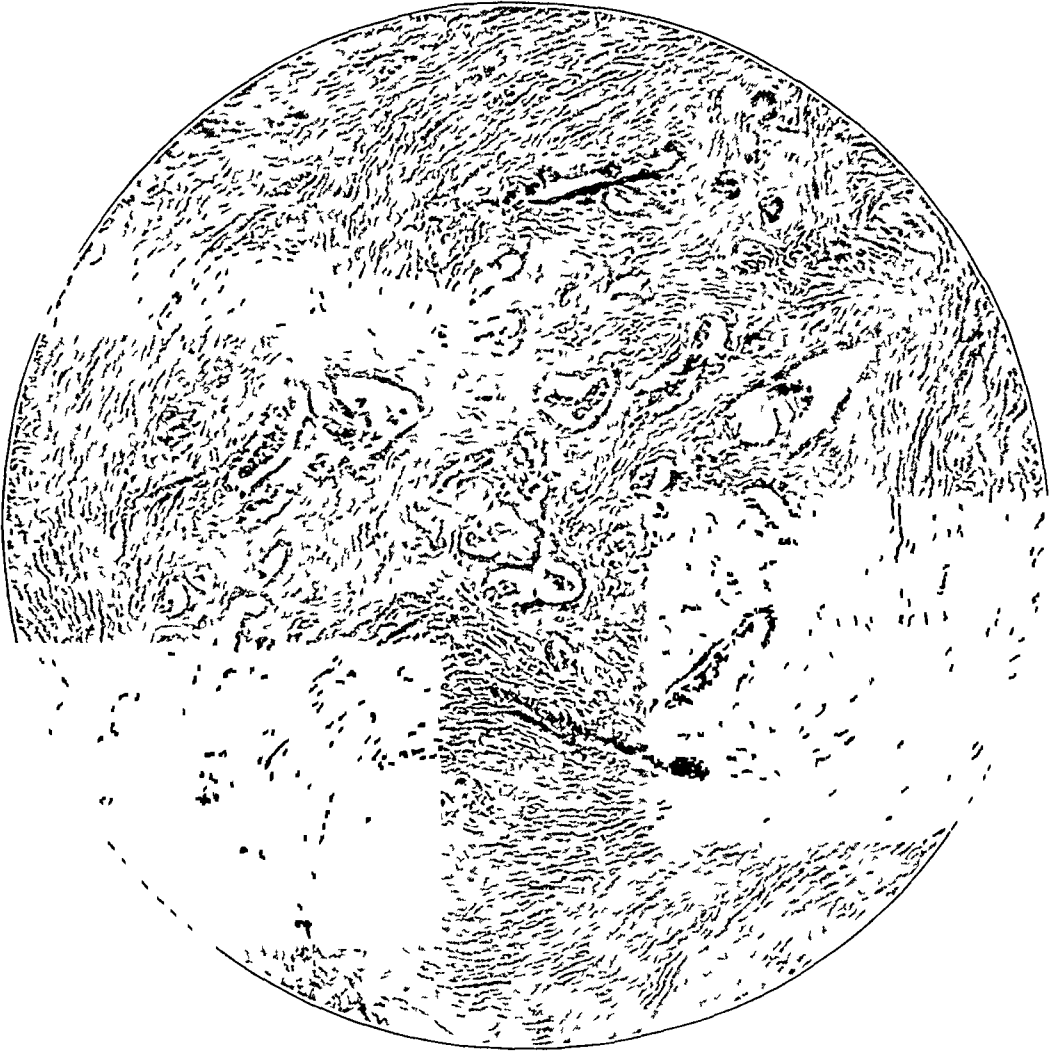


Fig 4—Fibrosis of the pancreas. Scattered remnants of dilated acini and ducts embedded within dense scar tissue are seen.

Report of Cases, *Am J Surg* **29** 85 (July) 1935. Haggard, W. D., and Kirtley, J. A., Jr. Pancreatic Calculi. Review of Sixty-Five Operative and One Hundred and Thirty-Nine Nonoperative Cases, *Ann Surg* **109**:809 (May) 1939.

35 (a) Hartwell, J. A., and Dudley, G. S. Abscess of the Lung, in Nelson's *New Loose-Leaf Medicine*, New York, Thomas Nelson & Sons, 1927, vol 3, p 503.
 (b) MacNalty, A. S., and Malloch, A. Influenza, *ibid*, vol 1, p 608.

36 Moolten, S. E. Mechanical Production of Cavities in Isolated Lungs, *Arch Path* **19** 825 (June) 1935.

the lungs by breathing, it enters these areas of tissue breakdown after purulent softening has taken place and expands them into rounded cavities many times their original size. Their expanded, rounded form is made permanent by subsequent fibrosis of their walls. An epithelial lining derived from the nearest draining bronchi replaces part of the pyogenic membrane, and, as a result, the sacculi often seem to resemble direct outgrowths of these bronchi instead of by-products of destruction of the lung tissue itself. Larger cavities, arising in areas of more extensive necrosis, are explained by the same mechanism. The ultimate size of such cavities is generally far greater than the original defect in the lung and is governed by the pressure of inspiration and of cough and by the degree of yielding of the surrounding fibroelastic framework.

Small patchy foci of necrotic softening occur not infrequently in lobar pneumonia,³⁷ particularly in infection with type III pneumococci^{37d} and the Friedlander bacillus,³⁸ and probably result from primary toxic injury by these organisms.^{37a} Somewhat less often a large circumscribed area of necrosis is encountered, which is apparently the result of ischemia from vascular thrombosis ("aputrid anemic necrosis").³⁹ Clinically, this lesion is discovered accidentally in the course of roentgen examination during convalescence from pneumonia, as it rarely produces clinical symptoms by itself. Its benign course and ultimate healing were first pointed out to me by Dr H. Wessler⁴⁰ and were made the subject of an excellent publication by Kessel.⁴¹

Infection by putrefactive anaerobic organisms pursues a distinctive course,⁴² typified in the familiar "putrid lung abscess." This is virtually

37 (a) Reimisch, M. Zur Entstehung der Pneumonienekrose, *Virchows Arch f path Anat* **290** 75 (Aug) 1933. (b) Letulle, M. *Anatomie pathologique*, Paris, Masson & Cie, 1931, vol 1, p 690. (c) Lauche, A. Die Entzündungen der Lunge und des Brustfelles, in Henke, F., and Lubarsch, O. *Handbuch der speziellen pathologischen Anatomie und Histologie*, Berlin, Julius Springer, 1928, vol 3, pt 1, p 758. (d) Finland, M., Brown, J. W., and Rueggsegger, M. Anatomic and Bacteriologic Findings in Infections with Specific Types of Pneumococci, Including Types I to XXXII, *Arch Path* **23** 801 (June) 1937. Finland, M., and Sutliff, W. D. Infections with *Pneumococcus* Type III and Type VIII, *Arch Int Med* **53** 481 (April) 1934. (e) Hartwell and Dudley.^{35a}

38 Bullowa, J. G. M., Chess, J., and Friedman, N. B. Pneumonia Due to *Bacillus Friedlanderi*. A Report on Forty-One Patients with Consideration of Specific Serum Therapy, *Arch Int Med* **60** 735 (Nov) 1937. Solomon, S. Primary Friedlander Pneumonia, *J A M A* **108** 937 (March 20) 1937. Sweany, H. C., Stadnichenko, A., and Henrichsen, K. J. Multiple Pulmonary Abscesses Simulating Tuberculosis, Caused by the Friedlander Bacillus, *Arch Int Med* **47** 565 (April) 1931.

39 Rosenthal, T. Ueber den Ausgang der fibrinösen Pneumonie in aputride anämische Nekrose, *Inaug Dissert*, Berlin, G. Schade, 1907. Lauche.^{37c}

40 Wessler, H. Personal communication to the author, 1928.

41 Kessel, L. The Clinical Aspects of Aputrid Pulmonary Necrosis, *Arch Int Med* **45** 401 (March) 1930.

a form of carbuncle with a central core of putrid necrosis. In its primary phase it is generally a solitary lesion. Rarely it presents itself as diffuse putrid gangrene of the lung. The principal distinguishing feature of putrid infection is its odor.

When infection is caused by a fungus or by one of the higher bacteria, destruction of lung tissue may be progressive and very extensive. Common examples are seen in infection with actinomyces,⁴³ the streptothrix⁴⁴ and, in weakened persons, the aspergillus⁴⁵

In the face of such a miscellany of causes of necrosis it is quite impossible to set it up as a landmark of classification in itself. However, when the occurrence of necrosis signifies something beyond its purely bacterial causation, such as a faulty degree of resistance by the host's tissues, it is useful to include it in the designation of the infection. The term necrotic pneumonia should be employed descriptively provided the bacterial cause, when known, is prefixed or implied, e g, in streptothrix necrotic bronchopneumonia^{44c}

Taken as a group, necrotic pneumonias may defy differentiation from tuberculosis of the lung in their roentgen and clinical features. Tests of the sputum are usually diagnostic, and tuberculous caseation is easily distinguished at autopsy from the necrosis of other infections. One exception to this should be noted. In severely cachectic persons with terminal hyperacute tuberculosis, the caseous material may be much softer and more liquefied than ordinarily, and smears may reveal enormous numbers of tubercle bacilli. In such an instance the specific histologic features of tuberculous granulation tissue are lacking⁴⁶. In conformity with morphologic classification, the condition in these cases should be termed "tuberculous necrotic bronchopneumonia."

Necrosis in the presence of inflammation may be stated generally to depend on two factors, the destructiveness of the bacterial agent and the destructibility of the host's tissue. The former is of concern here only in so far as it defines the specific character of the infection. The latter

42 Neuhof, H, and Wessler, H. Putrid Lung Abscess, *J Thoracic Surg* **1** 637 (Aug) 1932. Touroff, A S W, and Moolten, S E. The Symptomatology of Putrid Abscess of the Lung, *J Thoracic Surg* **4** 558 (Aug) 1935.

43 Arndt, H J. Die aktinomykotischen Veränderungen der Lunge und des Brustfells und das Verhalten der Lunge und des Brustfells bei Aktinomykose, in Henke, F, and Lubarsch, O. *Handbuch der speziellen pathologischen Anatomie und Histologie*, Berlin, Julius Springer, 1931, vol 3, pt 3, p 397.

44 (a) Arndt, H J. Die Streptotrichose der Lunge und des Brustfells, in Henke, F, and Lubarsch, O. *Handbuch der speziellen pathologischen Anatomie und Histologie*, Berlin, Julius Springer, 1931, vol 3, pt 3, p 459. (b) Moolten, S E. Streptotrichotic Suppuration of the Lung Following Aspiration of a Foreign Body, *J Mt Sinai Hosp* **1** 147 (Nov-Dec) 1934. (c) Page, I H. Streptothrix Necrotic Bronchopneumonia, *Arch Int Med* **41** 127 (Jan) 1928.

45 Moolten, S E. A Case of Primary Broncho-Pulmonary Aspergillosis, *J Mt Sinai Hosp* **5** 29 (May-June) 1938. Footnote 22.

46 Moolten, S E. Unpublished data.

is the chief factor which governs the outcome in the individual case. Constitutional factors deserve particular attention in all considerations pointing to this end, both when necrosis is characteristic of the infection and when it is not. The relation of diabetes to the development or aggravation of necrosis has already been discussed. The theory of that relation is based on cellular suboxidation leading to loss of vital potencies. Other forms of pronounced debility predispose to the same result, whether due to senility, undernutrition, uremia or extensive malignant disease.

ACUTE SUPPURATIVE BRONCHOPNEUMONIA

Neuhof and others⁴⁷ have recently directed attention to certain forms of bronchopneumonia complicated by an unusual degree of suppuration. Because of their apparently increased incidence and tendency to abscess formation they have been grouped together as a clinical entity under the title "acute suppurative bronchopneumonia." These are encountered as a complication of grip, purulent sinusitis, whooping cough, measles or bronchial obstruction. They may follow contamination of the bronchi by aspirated secretions or vomitus. Within the inflamed lobe or lobes multiple areas of softening occur. These form cavities of the order of saccular bronchiectases or larger or coalesce to form enormous solitary cavities which simulate pyopneumothorax in the roentgen film. Expectoration is copious, but the sputum is not foul. Empyema and pyopneumothorax may follow and may require surgical drainage. A fatal outcome is not uncommon, although in some cases the lesions undergo unexpected spontaneous disappearance, with complete recovery.

Complete pathologic study has been possible in a limited number of cases. From the descriptions given it appears that in certain instances the lesion is undoubtedly a form of necrotic bronchopneumonia like that complicating influenza. In cases of this sort, suppuration follows in the wake of necrosis. A variety of aerobic organisms has been found, including pneumococci, streptococci, staphylococci and the Friedlander bacillus, as well as certain anaerobic diphtheroids and streptococci. It is not clear at present how many of these are to be regarded as secondary invaders. In other instances it is possible that the lesion should be classified as a form of hyperacute interstitial bronchopneumonia in which suppuration is part of phlegmonous inflammation and probably caused by hemolytic streptococci.

47 (a) Neuhof, H, and others. Complications and Sequelae of Suppurative Bronchopneumonia, *J Mt Sinai Hosp* 3 36 (May-June) 1936. (b) Neuhof, H, and Touroff, A. S. W. Acute Aerobic (Nonputrid) Abscess of the Lung, *Surgery* 4 728 (Nov) 1938. (c) Sussman, M. L. Non-Putrid Pulmonary Suppuration, *Am J Roentgenol* 40 22 (July) 1938. (d) Rabin, C. B. *Radiology of the Chest*, in Golden, R. *Diagnostic Roentgenology*, New York, Thomas Nelson & Sons, 1936.

Data concerned with constitutional factors of resistance (e g, diabetes) are not yet available

INTERSTITIAL AND DISSECTING PNEUMONIAS

An important feature of infections of the lung by hemolytic streptococci is their tendency to localize within the interstitial framework. Accordingly, the term interstitial pneumonia has been applied when the predominant inflammation lies within this framework, which includes the peribronchial and perivascular sheaths, the subpleural connective tissue and the interlobular and interlobar septums with their finer intralobar subdivisions⁴⁸

Dissecting pneumonia, as the term implies, is pulmonary inflammation in which portions of the lung become detached or "dissected" from supporting tissues. The affected tissue is broken up into small or large fragments which lie within cavities filled with blood and pus⁴⁹

The usual form of dissecting pneumonia occurs as a complication of acute interstitial pneumonia in which suppuration spreading into the lung from the pleura along interlobular and subpleural septums brings about the separation of fairly large blocks of parenchyma. This is often accompanied by suppurative mediastinitis and suppurative pleuritis with empyema. In this type, seen most often in childhood, cavities are produced which contain sequestrums of all or most of the substance of the inflamed lobe. Such sequestrums become softened and may be discharged piecemeal into the empyema cavity or may be coughed up. Interstitial suppuration may proceed along the peribronchial sheaths to produce a similar result.

DISSECTING NECROTIC PNEUMONIA

The term "dissecting necrotic pneumonia" was applied in 1921 by Letulle and Bezançon⁵⁰ to a lesion similar to that observed in the present case. The extent of the lesion over an entire lobe, the dissecting type of necrosis, the absence of foul odor, the mixed bacterial flora and the clinical findings set this type of necrotic pneumonia apart from "putrid lung abscess" or gangrene and from various other specific infections, such as the mycoses. The extent of tissue destruction is far greater and far less circumscribed than that of the "aputrid necrosis," or small patchy necrotic areas, already mentioned, which may complicate ordinary lobar pneumonias. Its closest counterpart is seen in certain of the cases reported as examples of "acute suppurative bronchopneumonia" in which the destructive process involves nearly an entire lobe, with production of an enormous nonputrid abscess^{47b}

48 Lauche,^{37c} p 835

49 (a) Letulle,^{37b} p 687 (b) André, L. La pneumonie disséquante, Thesis, Paris, no 294, Paris, Jouve & Cie, 1920 (c) Lauche⁴⁸

50 Letulle, M., and Bezançon, F. La pneumonie disséquante necrotique, *Ann de med* 12 1 (July) 1922

The clinical picture of dissecting necrotic pneumonia was more or less consistent in the 4 cases described by Letulle and Bezançon. The onset was marked by sudden chill, high fever, pain in the chest, severe dyspnea and intense toxemia. Despite these evidences of pneumonia, early physical signs were meager and for the most part consisted in scattered coarse rales and harsh breath sounds. At first the sputum was mucopurulent and moderate in amount. After ten to twenty days the patient was seized with violent cough and quickly emptied his lungs of an enormous quantity of bloody purulent liquid of reddish brown or chocolate color. From then on the sputum remained hemorrhagic and had a stale, musty or garlic-like odor, but it was not foul. Signs of cavitation were then obtained, and roentgenograms showed an enormous vomica with a broad fluid level which could be mistaken for hydropneumothorax because of its size. In all 4 cases the condition was fatal.

Necropsy studies of these cases appeared to indicate that the underlying process was coagulative necrosis occurring in already consolidated lung. This was succeeded by a stage of intense leukocytic infiltration and digestion followed by liquefaction and cavity formation. Various stages coexisted side by side. The cavities were irregular and were lined with shaggy sloughs and fragments of lung tissue. These had become detached in whole or in part from more resistant structures, such as the bronchi and septums, and produced the appearance of massive sequestration, or "dissection." The distribution of the necroses did not follow anatomically predetermined patterns, however, as in the interstitial forms of dissecting pneumonia or the necroses caused by vascular closure. With the spread of the process the cavities enlarged and coalesced until almost the entire lobe was converted into one huge cavity containing brownish fluid and sloughing sequestrums of tissue. A minor degree of carnification occurred in the edges of the lesion, and the overlying pleura became greatly thickened and adherent. Blood vessels overtaken by the advance of the lesion were destroyed or thrombosed.

So far as causation is concerned, the striking feature of the disease was the luxuriant growth of a variegated mixed flora without predominant type. Pneumococci were not observed regularly, and other organisms, such as the Friedlander bacillus and various streptococci, were regarded as incidental contaminants. Among other things, the authors stressed the great importance of physical debility as an etiologic factor. Three of their patients were persons past middle age, and the fourth, a man aged 24, had chronic tuberculosis and diabetes mellitus. In a fifth case, reported later by Roubier and others,⁵¹ the condition occurred

51 Roubier, C., Froment, R., and Planchu, M. Vaste cavité purulente intrapulmonaire occupant la totalité du lobe supérieur gauche, chez un diabétique, *Lyon med* 147 313 (March 8) 1931.

in a diabetic patient aged 67 Peutz's²⁹ case of pancreatic calculus, which has been described, apparently falls into the same category Two cases reported by Neuhoft and Touroff^{47b} (cases 9 and 10) are probably also instances of this type

On the basis of its morphologic features it would seem desirable to include the condition in the present case among the foregoing ones As is noted in the autopsy protocol, the entire upper lobe of the right lung was in part consolidated and in part necrotic Large masses of lung tissue had become sequestered, forming irregular sloughs within cavities These were filled with nonodorous fluid and swarmed with a mixture of micro-organisms which resembled the saprophytic flora of decaying tissue

The unusually high incidence of pulmonary tuberculosis in cases of pancreatic calculus has already been mentioned In the present case tuberculosis was an inconspicuous part of the final picture, but seemed to have been reactivated to a limited degree by the necrotic pneumonia The latter may possibly have owed its localization within the upper lobe of the right lung to preexistent latent tuberculosis, and it is possible, too, that latent tuberculosis played a part in reducing the general vitality of the patient

"DIABETIC NONPUTRID GANGRENE OF THE LUNG"

The development of the modern treatment of diabetes mellitus has altered considerably the relative incidence of its principal factors of morbidity and mortality Whereas infection formerly stood in the first rank, its position has been largely superseded by complications of much slower development, especially arteriosclerosis

This change is nowhere better reflected than in the limited emphasis now placed on the pulmonary complications of diabetes, as contrasted with that shown in older treatises While pulmonary tuberculosis still occupies a major position, little mention is now made of other varieties of diabetic pneumopathy, especially that referred to as "diabetic gangrene of the lung" Naunyn,^{19e} Fraenkel^{19d} and others^{19a} described a condition not unlike dissecting necrotic pneumonia under this heading In its onset it resembled severe lobar pneumonia with hemorrhagic sputum which was almost never foul and with fatal termination in a few weeks Multiple foci of necrosis were seen in the lung at autopsy, usually with one of large size These areas were brownish red or grayish white, odorless and either softened or suppurating The surrounding tissue was consolidated Mixed bacterial growth was observed, as well as yeasts A peculiar softening of the lung was also described by several authors,⁵²

⁵² Kaufmann, E. *Lehrbuch der speziellen pathologischen Anatomie*, ed 7-8, Berlin, W de Gruyter & Co, 1922, vol 2, p 319 Beitzke, H. *Atmungsorgane*, in Aschoff, L. *Pathologische Anatomie*, ed 6, Jena, Gustav Fischer, 1923, vol 2, p 279 Rosenthal³⁹

under the title of "diabetic pneumomalacia" Infection and vascular occlusions apparently played little or no primary part This lesion was described as a putrid necrosis of pale color and "tinder-wood" appearance, often honeycombed with cavities and usually confined to small circumscribed areas but at times comprising a considerable extent of brownish red rotting tissue without odor Superinfection with saprophytic organisms from the upper air passages occurred frequently Fraenkel^{19d} suggested that nonputrid gangrene of the lung is a special form of diabetic pneumomalacia

In the last analysis the various forms of nonputrid "diabetic gangrene of the lung" can be resolved into one or another of the categories of necrotic pneumonia of nonspecific (mixed) bacterial causation It is a needless refinement of classification to individualize them on the basis of diabetes, since, as has been indicated, untreated diabetes is only one of many factors of lowered tissue resistance by which these necrotic pneumonias are linked Dissecting necrotic pneumonia, while morphologically distinctive, cannot be separated etiologically on any basis but one of degree Similarly, the mixed flora swarming in the sloughs of this lesion are to be regarded as opportunistic invaders of secondary virulence or as saprophytes, such as are seen in any decaying tissue

SUMMARY

The impaired resistance to infection in diabetic persons is probably part of a general vulnerability of diabetic tissues to injury of any type and is related to deficient cellular oxidation Both cellular repair and immunity responses may be seriously affected

The unfavorable prognosis of pulmonary tuberculosis in cases of poorly treated diabetes is well known Other pulmonary infections may also prove disastrous, particularly those which invite suppuration and necrosis Of peculiar interest is the predisposition of patients with prolonged pancreatic insufficiency to pulmonary suppuration and pulmonary tuberculosis The former is frequent in cases of congenital steatorrhea associated with fibrosis of the pancreas, the latter, in cases of pancreatic lithiasis

A case of pancreatic lithiasis is described in which chronic pancreatic insufficiency with diabetes mellitus was complicated by extensive necrotic pneumonia of mixed bacterial type Only 1 similar case has been reported in the literature This type of pneumonia appears to be identical with that described by Letulle and Bezançon under the heading of "dissecting necrotic pneumonia" and differs from other forms of necrotic and suppurative pneumonia in its distinctive morphologic and clinical features As in the present case, it is probably to be regarded as a special instance of the particular disposition of cachetic tissues to undergo necrosis

STRUCTURAL CHANGES IN THE ARTERIOLES OF THE MYOCARDIUM IN DIFFUSE ARTERIOLAR DISEASE WITH HYPERTENSION GROUP 4^{*}

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That diffuse arteriolar changes occur in the presence of essential hypertension seems well established. However, controversy exists concerning the exact nature, distribution, frequency of occurrence and severity of these changes.

Numerous investigators (Keith, Wagener and Kernohan,¹ Cain,² Moritz and Oldt,³ Fishberg,⁴ Pilcher and Schwab,⁵ Morlock,⁶ and others) have studied the changes occurring in the arterioles of selected organs in cases of hypertension. It has been reported by some investigators (Fishberg, Pilcher and Schwab) that when hypertension is present the changes noted in the arterioles of other organs almost never are observed in the arterioles of the myocardium.

LITERATURE

The first suggestion as to the occurrence of vascular change in association with hypertension was embodied in the observation of Bright.⁷

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* Some objection has been raised to the use of the term "malignant hypertension." In the following report, the terms "diffuse arteriolar disease with hypertension group 4" and "malignant hypertension" have been used interchangeably.

Abridgment of a thesis submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Medicine (Work done in the Section on Pathologic Anatomy)

1 Keith, N M, Wagener, H P, and Kernohan, J W. The Syndrome of Malignant Hypertension, *Arch Int Med* **41** 141-188 (Feb) 1928

2 Cain, E F. Malignant Hypertension. The Histologic Changes in the Kidneys, *Arch Int Med* **53** 832-850 (June) 1934

3 Moritz, A R, and Oldt, M R. Arteriolar Sclerosis in Hypertensive and Non-Hypertensive Individuals, *Am J Path* **13** 679-728 (Sept) 1937

4 Fishberg, A M. Anatomic Findings in Essential Hypertension, *Arch Int Med* **35** 650-668 (May) 1925

5 Pilcher, J F, and Schwab, E H. Arteriolar Changes in Essential Hypertension, *Texas State J Med* **28** 665-668 (Feb) 1933

6 Morlock, C G. Arterioles of the Pancreas, Liver, Gastro-Intestinal Tract and Spleen in Hypertension, *Arch Int Med* **63** 100-118 (Jan) 1939

7 Bright, R. Cases and Observations, Illustrative of Renal Diseases Accompanied with the Secretion of Albuminous Urine, *Guy's Hosp Rep* **1** 338-400, 1836

in 1836 that certain patients who had chronic Bright's disease also had noticeable thickening of the blood vessels

Johnson,⁸ in 1850, observed thickening of the arteriolar walls of the kidney in the presence of chronic Bright's disease, and he⁹ later demonstrated the existence of similar changes in the arteriolar walls of skin, skeletal muscle, intestine and pia mater

Johnson expressed the belief that this thickening is caused by hypertrophy of the muscular elements of the tunica media, and he concluded that arteriolar spasm is an important factor. Primary renal degeneration, in his opinion, leads to retention of urinary constituents in the blood, and, because the peripheral arterioles resist the flow of impure blood, the heart is called on to beat against an increased peripheral resistance. This process, he reasoned, results in simultaneous hypertrophy of the arteriolar walls and of the left ventricle of the heart.

Four years later, Gull and Sutton¹⁰ confirmed Johnson's observations but expressed the opinion that arteriolar thickening is caused not by hypertrophy of the medial musculature but by a hyaline fibroid degenerative change to which they applied the term "arterio-capillary fibrosis," a change which could be demonstrated in the kidney, brain, retina, spleen and skin. Gull and Sutton¹⁰ concluded that contraction and atrophy in the kidney referable to vascular changes are only part of a generalized vascular change and that, although the changes commonly originate in the kidney, they may also be primary in other organs.

Mahomed¹¹ observed that an elevated blood pressure may exist for some time in the absence of any signs of damage to the kidneys. He labeled this phase "the pre-albuminuric stage of chronic Bright's disease," but in reality he had discovered essential hypertension. He concluded that hypertension and the subsequent cardiovascular changes are the primary condition and that renal symptoms are secondary. Mahomed stated that certain cases occur in which the cardiovascular changes associated with Bright's disease are present but in which no marked changes can be discovered in the kidneys.

8 Johnson, G. On the Proximate Cause of Albuminous Urine and Dropsy, and on the Pathology of the Renal Blood-Vessels in Bright's Disease, *Tr Roy Med-Chir Soc London* **33** 107-120, 1850.

9 Johnson, G. I. On Certain Points in the Anatomy and Pathology of Bright's Disease of the Kidney, II. On the Influence of the Minute Blood-Vessels upon the Circulation, *Tr Roy Med-Chir Soc London* **51** 57-76, 1868.

10 Gull, W. W., and Sutton, H. G. On the Pathology of the Morbid State Commonly Called Chronic Bright's Disease with Contracted Kidney, *Tr Roy Med-Chir Soc London* **55** 273-326, 1872.

11 Mahomed, F. A. The Etiology of Bright's Disease and the Prealbuminuric Stage, *Tr Roy Med-Chir Soc London* **57** 197-228, 1874, Some of the Clinical Aspects of Chronic Bright's Disease, *Guy's Hosp Rep* **24** 363-436, 1879.

Ewald's¹² observations, made in 1877, confirmed the presence of medial hypertrophy as described by Johnson. Ewald particularly stressed thickened arteriolar walls and narrowed lumens, and he emphasized that the increase in thickness of the wall is caused by a simple increase in the number of muscle fibers.

Jores¹³ observed hyaline and fatty changes in the intima and hyperplasia of the internal elastic lamina in the visceral arterioles of hypertensive patients. These changes, he found, had led to a narrowing of the lumens of the arterioles and had occurred most frequently in the arterioles of the kidney, brain, spleen, pancreas and intestine. Jores was unable to demonstrate any change in the arterioles of skeletal muscle.

He concluded that when a diffuse arteriolar lesion is present it is degenerative and is limited to the intima. He strongly denied the existence of muscular hypertrophy; instead, he emphasized the process as one of arteriosclerosis. Like Gull and Sutton, Jores expressed the opinion that the vascular changes are widespread, sometimes leading to renal disease and at other times to cardiac or cerebral failure with normal renal function.

In 1914, Volhard and Fahr¹⁴ postulated the existence of a toxic factor which, when superimposed on the arteriosclerotic changes associated with benign hypertension, produces the malignant form of the disease. Volhard¹⁵ later repudiated the theory that the vascular and glomerular changes found in the presence of malignant hypertension are inflammatory, and he expressed the belief that the lesions are the result of ischemia brought about by prolonged vascular spasm.

Fahr¹⁶ likewise revised his ideas on the subject and expressed his later conviction that benign hypertension is the result of simple arteriosclerosis of the larger arterioles and malignant hypertension the result of inflammatory and necrotic arteriolar changes on a toxic basis. He

12 Ewald, C. A. Ueber die Veränderungen kleiner Gefäße bei Morbus Brightii und die darauf bezüglichen Theorien, *Virchows Arch f path Anat* **71** 453-499 (Dec) 1877.

13 Jores, L. Ueber die Arteriosklerose der kleinen Organarterien und ihre Beziehungen zur Nephritis, *Virchows Arch f path Anat* **178** 367-406, 1904, Ueber den pathologischen Umbau von Organen (Metallavie) und seine Bedeutung für die Auffassung chronischer Krankheiten insbesondere der chronischen Nierenleiden (Nephrozirrhosen) und der Arteriosklerose, nebst Bemerkungen über die Namengebung in der Pathologie, *ibid* **221** 14-38, 1916.

14 Volhard, F., and Fahr, K. T. Die Brightsche Nierenkrankheit, Klinik, Pathologie und Atlas, Berlin, Julius Springer, 1914.

15 Volhard, F. Der arterielle Hochdruck, *Verhandl d deutsch Gesellsch f inn Med* **35** 134-175, 1923.

16 Fahr, T. Ueber Nephrosklerose, *Virchows Arch f path Anat* **226** 119-178, 1919, Ueber die Beziehungen von Arteriolenklerose, Hypertonie und Herzhypertrophie, *ibid* **239** 41-63, 1922.

minimized the inflammatory nature of the glomerular lesions and emphasized the inflammatory vascular lesions, which he chose to designate as "necrotizing arteriolitis"

Allbutt,¹⁷ in 1915, stated that in his opinion hypertension may exist for years without the appearance of any signs of renal damage and that death may eventually occur as the result of cerebral or cardiac failure. He expressed the belief that "hyperpiesia" is caused by a dynamic factor rather than by an organic narrowing of the peripheral arterioles but that elevation of the blood pressure over a long period may result in generalized arteriolar thickening.

Wagener and Keith,¹⁸ in 1924, reported a series of 14 cases of marked hypertension, severe retinitis and adequate renal function. In all cases death occurred within forty-four months after the onset of symptoms. Because of this, Wagener and Keith proposed the term "malignant hypertension" for the condition.

Fishberg expressed the belief that the earliest pathologic change occurring in essential hypertension is the deposition in the afferent arterioles of the kidney of hyalin, which later undergoes fatty change. In larger vessels a hyperplastic intimal thickening takes place, with subsequent hyalinization and proliferation of surrounding connective tissue, which leads to narrowing and possibly to complete obliteration of the lumen. The tunica media, Fishberg said, shows little or no change until late in the process, when it undergoes atrophy and fibrosis. In his opinion, the renal arterioles are involved more frequently than are those of any other organ. He observed changes in the arterioles of the myocardium in only 2 of 68 cases studied, and he was unable to demonstrate structural changes in the arterioles of skeletal muscle.

Keith, Wagener and Kernohan,¹⁹ in 1928, reported 81 cases of malignant hypertension. It was of interest to the authors that many patients died as a result not of failure of one vital organ but of simultaneous failure of several organs, for example, of cerebral, cardiac and renal failure. Seven patients came to necropsy, and the arteriolar changes were noted. Microscopically, the arterioles exhibited marked hyperplasia of the intima and hypertrophy of the tunica media and internal elastic lamina. Perivascular fibrosis was present in varying degrees. There were almost no signs of degenerative change.

17 Allbutt, T. C. *Diseases of the Arteries Including Angina Pectoris*, London, Macmillan Company, Ltd., 1915, vol. 1, pp. 378-454.

18 Wagener, H. P., and Keith, N. M. Cases of Marked Hypertension, Adequate Renal Function and Neuroretinitis, *Arch Int Med* **34** 374-387 (Sept.) 1924.

19 Keith, N. M. Classification of Hypertension and Clinical Differentiation of the Malignant Type, *Am Heart J* **2** 597-608 (Aug.) 1927. Keith, Wagener and Kernohan.¹

The investigators stressed especially the diffuse and widespread involvement of all organs by the process, the medial hypertrophy and the intimal thickening, and they expressed the opinion that the thickening, if steadily progressive, ultimately would lead to occlusion of the lumen of the arteriole. In their opinion, this fact supports Volhard's ischemic theory and offers a logical explanation for the diffuse parenchymatous lesions associated with this syndrome.

Like Fishberg, Bell and Clawson²⁰ expressed the opinion that marked hyperplastic intimal thickening of the afferent glomerular arteries is almost conclusive evidence of the presence of hypertension and that this thickening rarely occurs in the absence of hypertension.

In 1929, Kernohan, Anderson and Keith²¹ made a histologic study of the changes in the arterioles of specimens of pectoral muscle taken for biopsy from 53 patients who had hypertension, the hypertension of 11 patients being benign, that of 18 patients severe benign (or early malignant) and that of 23 patients malignant. The condition of the 1 remaining patient, who had chronic glomerulonephritis, was studied for comparison with the condition of other patients, who had diffuse arteriolar disease with hypertension. Material for controls was obtained from pectoral muscles of patients without hypertension and at necropsy from patients without elevated blood pressure or cardiac enlargement. The mean normal wall to lumen ratio was found to be 1.2, with variations from 1.17 to 1.27. In cases of benign hypertension the mean ratio was 1.14, with variations from 1.11 to 1.18. In cases of severe benign and malignant hypertension the mean ratio was 1.11, with variations from 1.09 to 1.17. There was slight increase in the perivascular connective tissue. The most pronounced and most usual change was hypertrophy of the tunica media with an increase in the nuclear elements. They noted no medial fibrosis and almost no evidence of degenerative change. There were hyperplasia and, in some cases, splitting of the internal elastic lamina. The intimal changes were varied, but the most constant finding was proliferation of the endothelial and subendothelial cells, sometimes to such a degree that the lumen was almost completely occluded.

In 1931, Klemperer and Otani²² analyzed 16 cases of malignant nephrosclerosis and concluded that the primary lesion was arteriosclerosis of the small renal vessels. They stated that there were two

20 Bell, E. T., and Clawson, B. J. Primary (Essential) Hypertension. A Study of Four Hundred and Twenty Cases, *Arch Path* 5: 939-1002 (June) 1928.

21 Kernohan, J. W., Anderson, E. W., and Keith, N. M. The Arterioles in Cases of Hypertension, *Arch Int Med* 44: 395-423 (Sept.) 1929.

22 Klemperer, P., and Otani, S. "Malignant Nephrosclerosis" (Fahr), *Arch Path* 11: 60-117 (Jan.) 1931.

distinct types, one of which was a slowly progressive form of sclerosis producing a gradual constriction of the vascular bed with destruction of renal parenchyma and the other a rapidly developing vascular change with which there was no marked atrophy of the kidneys

Keith, Barker and Kernohan ²³ in 1931 made a histologic study of the arterioles of pectoral muscle of 143 patients suffering from hypertensive disease. Their group 1 included 11 patients who had chronic glomerulonephritis with hypertension. Arteriolar changes as described by Kernohan, Anderson and Keith were found to affect 4 of the 11 patients (36 per cent). Groups 2, 3, 4 and 5 corresponded to groups 1, 2, 3 and 4, respectively, as described by Keith, Wagener and Kernohan. Keith, Barker and Kernohan concluded from their observations that the anatomic changes in the arterioles in the presence of hypertensive disease occur more often among patients with severe hypertension but that the changes are not in proportion to the duration or elevation of the blood pressure.

Scott, Seecof and Hill, ²⁴ in 1933, demonstrated that the appearance of specimens of skeletal muscle obtained for biopsy from hypertensive patients was practically the same as that of specimens from the same patients when eventually they came to necropsy and that the intensity of the arteriolar lesions in the kidney agreed closely with that observed in the specimens of skeletal muscle at both biopsy and necropsy.

Pilcher and Schwab studied the arteriolar changes in various organs of 15 patients with hypertension and observed a significant decrease in the wall to lumen ratios for all organs except the myocardium. They could not explain the absence of changes in the myocardial arterioles but suggested as a possible explanation that the demand for increased blood supply by the hypertrophied heart might have resulted in the formation of new blood vessels.

Cain, in 1933, made a study of the pathologic changes in the renal arterioles of 27 patients with malignant hypertension, and he observed an apparent increase in the number of endothelial cells in each instance, with subendothelial, fatty and hyaline degeneration, an apparent thickening of the media and an increase in perivascular connective tissue. The wall to lumen ratios of the renal arterioles were reduced to less than 1:10 in all but a single instance.

Moritz and Oldt have concluded from their study of the arteriolar changes associated with hypertension that intimal hyalinization, medial

²³ Keith, N. M., Barker, N. W., and Kernohan, J. W. Histologic Studies of the Arterioles in Various Types of Hypertension, *Tr. A. Am. Physicians* **46** 66-70, 1931.

²⁴ Scott, R. W., Seecof, D. P., and Hill, A. A. Arteriolar Lesions of Skeletal Muscle in Hypertension, *Tr. A. Am. Physicians* **48** 283-288, 1933.

hypertrophy and degeneration and intimal proliferation are the three principal changes characterizing the disease. Lesser degrees of thickening are felt to be the result of medial hyperplasia, whereas more advanced thickening is the result of degeneration and thickening of the tunica media and intima. Moritz and Oldt concluded that these changes occur in direct proportion to the size of the arteriole and that the decrease in the wall to lumen ratio is caused not by narrowing of the lumen but by increased thickness of the wall. The difference in this ratio between the hypertensive and the nonhypertensive group was not sufficient in 80 per cent of the cases to permit distinction, but in more than 80 per cent of the cases the hypertensive and the nonhypertensive patients could be classified as such by the presence or absence of changes in the arteriolar walls. Moritz and Oldt also emphasized the segmental distribution of the pathologic changes in the arterioles of skeletal muscle.

Morlock has made a study of the arteriolar changes occurring in the liver, pancreas, intestinal tract and spleen of a series of patients with hypertension. He observed significant arteriolar changes in all the organs he studied. On the basis of pathologic change, he has shown the degree of thickening to be as pronounced in one organ as it is in another. He has demonstrated clearly that the degree of thickening and the amount of structural change in various arterioles increase with the severity of the disease and that the least degree of change occurs in the presence of benign hypertension, whereas the most profound changes are seen when the malignant form is present.

Recently, Rosenberg²⁵ has completed a study of vascular changes in the brain in the presence of severe hypertension and has shown that in patients with malignant hypertension the cerebral arterioles undergo luminal narrowing and that thickening and structural changes of the walls take place, similar to the changes described as occurring in other organs.

CLINICAL OBSERVATIONS

Forty-eight patients having diffuse arteriolar disease with hypertension group 4, or so-called malignant hypertension, were studied clinically. Thirty-three of the 48 patients were males, and 15 were females. The ages ranged from 7 to 75 years, the average being 43.5 years, but the majority of patients were between the ages of 40 and 60 years. The number of patients in each decade is given in table 1.

The duration of known hypertension varied from one month to ten years, with an average of two years and four months. Eight patients did not know they had hypertension until it was discovered on physical examination.

²⁵ Rosenberg, E. F. Personal communication to the author.

Three patients had a history of chronic glomerulonephritis which had been diagnosed five, six and seven years, respectively, prior to the onset of symptoms of malignant hypertension

A survey of family histories revealed cerebral accident in 20 cases, cardiac failure or coronary occlusion in 12 and renal disease in 4. Six patients had living relatives with hypertension. The family history was irrelevant in 11 cases and unknown in 6.

The patients were placed in four groups, "cardiac," "renal," "cerebral" and miscellaneous, according to the predominant symptoms and observations. Abstracts of 3 illustrative cases are presented.

REPORT OF CASES

CASE 4—A man 49 years of age registered at the Mayo Clinic on Nov 13, 1924, complaining of dyspnea on exertion and orthopnea of two months' duration,

TABLE 1—*Distribution of Ages by Decades Forty-Eight Patients Having Diffuse Arteriolar Disease with Hypertension Group 4*

Decade	Patients	Per Cent
0-9	1	2.1
10-19	0	0
20-29	6	12.5
30-39	9	18.7
40-49	17	35.4
50-59	12	25.0
60-69	2	4.2
70-79	1	2.1
Total	48	100.0

accompanied by persistent productive cough. For the same length of time he had been extremely nervous and restless. He had lost 15 pounds (6.8 Kg.). For two weeks he had been troubled with edema of the extremities, nausea, vomiting, substernal pain on inspiration, blurring of vision and vertigo. The patient's maternal grandfather had died after a cerebral accident.

On examination the patient's weight was 114 pounds (51.7 Kg.), and he appeared acutely ill. There was a definite urinous odor to his breath. Peripheral vascular sclerosis was present and was graded 2. To percussion, the heart measured 4 by 14 cm., and both a systolic and a diastolic murmur were heard at the apex. The aortic second sound was accentuated. The patient was orthopneic and had cyanosis grade 2. Moist rales were heard over the bases of both lungs. The edge of the liver was palpable 6 cm. below the right costal margin. There was massive edema of the sacral region, genitalia and extremities. Examination of the fundi disclosed severe retinitis with bilateral papilledema.

The patient's condition became progressively worse, and a pericardial friction rub developed on the thirteenth day in the hospital. On the same day he lapsed into coma. He died two days later.

CASE 13—A farmer 48 years of age registered at the clinic on March 10, 1928, complaining of nocturia, frequency of urination and severe headaches of two and a half years' duration. At the onset, the patient had had a transient attack of

aphasia which had followed a severe headache. For six months he had noticed palpitation, dyspnea on exertion, orthopnea, precordial pain and frequent epistaxis. His father and a brother had died after cerebral accidents, his mother had died of congestive heart failure, and one brother had died of chronic glomerulonephritis.

On examination the patient weighed 159 pounds (about 72 Kg). Peripheral vascular sclerosis was present and was graded 2 to 3. The heart measured 25 by 11.5 cm. The aortic second sound was accentuated (grade 2), there were a basal systolic murmur and a questionable apical systolic murmur. The patient had severe retinitis with bilateral edema of the optic disks.

He returned on May 13, complaining of nausea and vomiting, marked dyspnea on exertion, orthopnea, precordial pain, hemoptysis, oliguria, vertigo and blurred vision of two weeks' duration. He had definite orthopnea and cyanosis. His peripheral vascular sclerosis was graded 4. The heart measured 2 by 13 cm. Both the aortic and the pulmonic sounds were accentuated, the pulmonic second sound being louder than the aortic second sound. The first sound was roughened, and there was a basal diastolic murmur. There were moist rales in the bases of both lungs. The retinal observations were unchanged.

The patient became progressively worse, and Cheyne-Stokes respiration developed, pericarditis, anuria, mental confusion and muscular twitchings occurred. He lapsed into coma and died on the eleventh day.

CASE 34—A grocer 52 years of age registered at the clinic in March 1932. He was found in the street in a comatose state, with cyanosis, vomiting and right hemiparesis. He had had three convulsions. On regaining consciousness he stated that he had had occasional episodes of blurred vision, "pressure in the head" and substernal oppression for four years.

On examination peripheral sclerosis was present and was graded 2 to 3, it was of the rubbery type. There was an apical systolic murmur, but otherwise the results of examination of the heart were negative. Examination of the ocular fundi revealed severe retinitis with hemorrhages, cotton wool exudates and edema of the optic disks.

The patient returned on five different occasions between March 1932 and April 1933, each time complaining of vertigo, tinnitus, headaches, failing vision, weakness and dyspnea on exertion. He had had several attacks of unconsciousness in the past year, varying in duration from one to twelve hours.

The patient returned in August 1933, at which time his peripheral sclerosis was graded 3. The heart was markedly enlarged to the left, the rhythm was grossly irregular, and a loud, blowing systolic murmur could be heard over all areas. Results of examination of the ocular fundi were the same as on previous admissions. On October 6 the patient had a sudden attack of weakness and dizziness and lapsed into coma. His respirations became stertorous, cyanosis developed, two tonic convulsions occurred, and the patient died.

In 20 cases the predominant symptoms were cerebral, in 21, cardiac, in 3, renal, and in 4, referable to the gastrointestinal tract. In 24 cases the earliest symptoms were cerebral, in 15, cardiac, and in 6, renal.

The most common symptoms were headaches occurring in the early morning, visual disturbances, dyspnea and tachycardia. Urinary symptoms were relatively infrequent. Loss of weight and strength were important features in the majority of cases.

TABLE 2—Laboratory Data on Forty-Eight Patients Having Diffuse Arteriolar Disease with Hypertension Group 4

Case	Sex	Age	Blood Pressure, Mm of Mercury				Urine			Blood									
			Maximum		Minimum		Specific Gravity	Albumin, Grade	Erythrocytes, Grade	Hemoglobin *	Erythrocytes, Millions per Cu Mm of Blood	Leukocytes per Cu Mm of Blood	Urea, Mg per 100 Cc of Blood	Creatinine, Mg per 100 Cc of Blood	Sulfates, Mg per 100 Cc of Serum	Chlorides, Mg per 100 Cc of Plasma	Plasma Carbon Dioxide-Combining Power, Vols per 100 Cc of Blood		
			Systolic	Diastolic	Systolic	Diastolic													
1	F	45	255	150	200	140	1 026	1	0	82%	5 11	13,000	34	1 9					
2	F	55	260	160	210	130	1 018	3	0	79%	4 00	10,400	33	1 8					
3	F	42	240	140	222	130				76%			134	7 4					
4	M	49	220	140	184	90	1 013	trace	0	56%	3 36	19,200	355	19 0					
5	M	46	238	155	170	90	1 023	3	0	67%	3 52	5,000	48	2 1		558	53		
6	M	65	240	140	188	108	1 018	1	0	61%	4 62	19,000	101	4 5		642	53		
7	F	46	294	176	170	96	1 015	4	occ	84%	3 30	24,400	204	8 8					
8	M	40	220	169	168	128	1 015	4	0	72%	4 00	16,200	518	17 0					
9	M	50	260	170	180	90	1 020	2	1	58%	3 17	32,400	158	7 1		530	23		
10	M	40	255	130	230	110	1 012	1	0	40%	2 56	8,200	242	10 4		640	55		
11	M	39	230	150	165	96	1 015	2	0	65%	3 48	10,900	382	9 6					
12	M	23	250	174	148	92	1 020	4	1	80%	4 96	11,800	40			528	18		
13	M	48	220	167	160	110	1 020	3	occ	73%	4 27	6,100	51	3 9					
14	M	60	220	152	170	110	1 015	2	0	40%	2 58	7,100	651	35 2	148 9	359	20		
15	M	75	220	132	205	112	1 010	3	1	58%	2 96	6,600	146	6 6					
16	F	57	300+	240	190	70	1 018	2	1	75%	4 77	5,000	44	1 6		585	84		
17	M	22	215	160	170	118	1 013	3	0	70%	4 50	18,200	110	3 0		537	50		
18	F	37	240	144	190	130	1 016	4	2	60%	3 04	12,000	252	6 4		568	63		
19	F	23	278	205	235	160	1 012	4	0	58%	3 46	10,800	36	1 9					
20	M	45	236	160	186	100	1 016	3	1	64%	3 68	19,600	246	9 6					
21	M	30	230	165	170	128	1 013	3	0	17 2 Gm	5 20	11,200	20			603	48 5		
22	M	39	220	156	158	94	1 012	3	2	40%	2 48	20,800	444	20 0		479	21 7		
23	M	40	160	80	112	70	1 030	0	0	15 9 Gm	4 56	12,100							
24	M	39	245	150	130	100	1 013	3	2	60%	3 33	17,200	132	2 4					
25	M	56	250	135	160	90	1 014	3	3	58%	3 03	19,800	243	9 2	18 9	462	46 6		
26	M	42	225	155	170	120	1 030	3	0	88%	4 20	9,300	40	1 5					
27	M	37	244	162	168	106	1 020	4	1	12 3 Gm	3 76	13,200	190	3 0	10 5				
28	M	56	206	140	136	92	1 038	4	4	13 3 Gm	4 69	10,200	38		5 1				
29	F	52	190	130	130	90	1 019	4	4	7 6 Gm	2 29	18,000	232	13 6	35 8	396	36 2		
30	F	26	160	100			1 011	2	1	71%	3 33	9,800	303	23 0	26 2	520	26 8		
31	F	37	280	175	154	100	1 026	4	0	76%	4 50	7,000	48	1 8	5 9				
32	F	35	245	160	144	90	1 018	4	3	58%	3 14	20,100	256						
33	M	32	350+	190	244	162	1 027	3	1	79%	4 67	7,500	18	1 1					
34	M	52	220	130	166	88	1 025	4	1	14 7 Gm	4 56	8,200	18						
35	M	29	240	150	164	75	1 025	2	2	80%	4 73	9,200	28	1 6	6 4				
36	M	54	220	150	160	110	1 000	3	0	15 2 Gm	4 85	17,250	34	8 4	6 8	561	47 5		
37	M	48	260	150	176	100	1 011	4	3	14 5 Gm	4 85	17,250	34	8 4	6 8	561	47 5		
38	M	54	290	190	184	110	1 011	4	3	15 2 Gm	4 85	17,250	34	8 4	6 8	561	47 5		
39	M	46	244	150	140	80	1 021	3	2	14 5 Gm	4 85	17,250	34	8 4	6 8	561	47 5		
40	F	47	270	170	210	116	1 021	3	2	14 5 Gm	4 85	17,250	34	8 4	6 8	561	47 5		
41	M	47	130	80			1 023	2	2	80%	4 54	8,100	38	1 8					
42	M	57	230	175	146	108	1 025	2	1	15 7 Gm	4 30	8,200	34						
43	M	55	240	152	178	98	1 017	2	1	89%	3 75	6,100	38						
44	F	41	230	125	184	102	1 016	4	4	9 0 Gm	3 39	7,300	162	8 1	11 7	575	42 8		
45	F	7	238	190	136	74	1 021	3	1	14 5 Gm	3 57	6,400	116						
46	M	34	204	152	150	100	1 031	4	2	89%	4 56	8,300	42						
47	M	50	136	94			1 016	0	0	95%		6,800							
48	F	44	250	175	180	110	1 020	4	1	11 7 Gm	4 40	5,000	64	2 2	6 5	528	54 1		

* Hemoglobin is expressed in grams per hundred cubic centimeters of blood. The remaining values represent the per cent of hemoglobin by the Dare method.

Analysis of physical observations was directed especially to the cardiovascular system, and the results were in accord with the analysis made by Keith, Wagener and Kernohan. Marked elevation of blood pressure was observed in all cases. The maximal systolic reading varied from 170 to 350 mm of mercury, and the maximal diastolic, from 100 to 240 mm. In cases 31, 41 and 47 the blood pressure was normal on the first visit to the clinic, but on subsequent visits it was found to be elevated (table 2). Clinical evidence of anemia was noted infrequently. There was palpable enlargement of the thyroid gland in 3 cases. The grade of peripheral vascular sclerosis as determined by palpation of the brachial and radial arteries varied from 1 to 3. It was mild in 4 cases, moderate in 13 and marked in 20. Arterial occlusion in the extremities did not occur.

A diffuse purpuric eruption was noted in 6 cases. Meakins²⁶ has called attention to the purpuric manifestations and other hemorrhagic phenomena accompanying conditions associated with hypertension. He expressed the belief that these manifestations are caused by arteriolar or capillary vasoconstriction leading to slowing of the blood stream, or "prestasis," with subsequent diapedesis of erythrocytes into surrounding tissues.

Tachycardia was present in 42 of the 48 cases, and the heart was measurably enlarged to percussion in the same number of cases. Extrasystoles were encountered in 8 cases, auricular fibrillation in 4, gallop rhythm in 9 and pulsus alternans in 3.

The aortic second sound was accentuated in 31 cases and the pulmonic second sound in 7. Cardiac murmurs were heard in the majority of cases. In 28 cases there was an apical systolic murmur, and in 19, an aortic systolic murmur. An apical diastolic murmur was audible in 5 cases, and an aortic diastolic murmur in 2. A pericardial friction rub was heard in 10 cases. In 38 cases the patients exhibited signs of cardiac decompensation. The spleen was palpable in 2 cases.

Cheyne-Stokes respiration was noted in 20 cases. Muscular twitchings occurred in 11 cases and generalized convulsions in 4. Twelve patients had signs of involvement of the central nervous system. Signs of cerebrovascular accident were present in 11 cases. In case 32 there was a history of recurrent facial palsy, and the neurologic signs were those of facial paralysis without hemiplegia. In case 36 a tumor of a temporal lobe was suspected.

²⁶ Meakins, J. C. Arteriolar Infarction, *Ann Int Med* 8 661-668 (Dec) 1934

The retinal features characteristic of malignant hypertension as described by Wagener and Keith, with narrowing and sclerosis of the retinal arterioles and edema of the optic disks, were present in all 48 cases

LABORATORY DATA

The specific gravity of the urine varied from 1 000 to 1 038 In 16 cases the specific gravity exceeded 1 020 In cases 17, 23, 26, 27, 30, 31 and 41 it exceeded 1 020 on early admission to the clinic but was lower than 1 020 on subsequent determinations Albuminuria varied in grade from 1 to 4 In only 5 cases was the urine free from albumin In the majority of cases casts were present in the urine, and hematuria varied in grade from 1 to 4

If 80 per cent hemoglobin, or 12 Gm of hemoglobin per hundred cubic centimeters of blood, and 4,000,000 erythrocytes per cubic millimeter of blood are considered to be the lower limits of normal, it will be noticed that anemia in varying degree was present in the great majority of instances It is interesting to observe that the leukocyte count exceeded 9,000 per cubic millimeter of blood for more than half the patients

The serologic tests for syphilis gave negative results in 44 cases In cases 12, 38 and 31 the results were strongly positive, and in case 37 the reaction was indeterminate In case 12 the results of tests for syphilis performed on the spinal fluid were also strongly positive

If 40 mg of urea per hundred cubic centimeters of blood is considered to be the upper limit of normal, the terminal value for 43 patients was elevated In 7 cases the concentration of urea in the blood varied from 40 to 100 mg per hundred cubic centimeters Determinations of "terminal blood urea" in 25 cases revealed between 100 and 300 mg per hundred cubic centimeters In these 32 cases (7 plus 25) it is difficult to estimate how much of the elevation in the concentration of urea can be accounted for on the basis of renal insufficiency and how much was caused by congestion in the kidneys occurring as part of the picture of congestive heart failure In 11 cases the value for blood urea exceeded 300 mg per hundred cubic centimeters The value for the terminal concentration of blood creatinine was more than 2 mg per hundred cubic centimeters in 35 cases

Determinations of the values for serum sulfate were made in 23 cases In 19 the terminal value was above the upper limit of normal (5.5 mg per hundred cubic centimeters) In case 13, the value increased terminally to 148.9 mg per hundred cubic centimeters, which is the highest figure for serum sulfates on record at the Mayo Clinic

The value for plasma chlorides was normal in the majority of cases. The carbon dioxide-combining power of the plasma was measured in 31 cases. In only 13 cases did the value fall below 40 volumes per cent, indicating the presence of significant acidosis.

The rate of excretion of phenolsulfonphthalein in the urine was measured in 20 cases. In 11 cases, in two hours' time the patient excreted 50 per cent or more of the dye injected. In cases 8, 10, and 17 no dye was recovered in the urine.

TABLE 3—*Rates and Axis Deviations Forty-Nine Electrocardiograms Representing Thirty-Five Patients Having Diffuse Arteriolar Disease with Hypertension Group 4*

Rate	Tracings, Number	Axis Deviation	Tracings, Number
Sinus bradycardia	6	Left	39
Sinus rhythm	26	Right	1
Sinus tachycardia	17	None	9
Totals	49		49

TABLE 4—*Alterations in the RT Segments and T Waves Forty-Nine Electrocardiograms Representing Thirty-Five Patients Having Diffuse Arteriolar Disease with Hypertension Group 4*

Deviation		I	II	III	IV*
RT Segment	Depressed	37	21	5	3
	Isoelectric	12	24	18	0
	Elevated	0	4	26	0
	Total	49	49	49	3
T Waves	Inverted	24	14	16	2
	Diphase	12	16	3	1
	Isoelectric	1	2	0	0
	Upright	12	17	30	0
Total		49	49	49	3

* Only three tracings of deviation IV were made.

The laboratory data for each patient are given in table 2.

Forty-nine electrocardiograms representing 35 cases were studied, and the results are given in tables 3 and 4. It is of interest that in case 8 right axis deviation was observed. In this case there was a presystolic murmur which was transmitted to the tricuspid area, but no other signs of rheumatic heart disease were present. However, at necropsy the mitral valves were found to be markedly thickened, and there was hypertrophy of both ventricles, with marked dilatation of the right.

The tracings in cases 12 and 15 showed T waves in derivations I and II suggestive of coronary occlusion, but this condition was not confirmed either clinically or pathologically. In case 48, diminished Q waves were noted in derivation IV. The sudden death of the patient suggested

the presence of coronary occlusion or cerebral accident, but at necropsy no signs of coronary thrombosis were discovered

Although the results were variable, table 4 indicates that the majority of tracings showed depression of the RT segment, that inverted T waves predominated in derivation I, that a depressed or isoelectric RT segment predominated in derivation II and that the majority of tracings showed an elevation of the RT segment, with upright T waves, in derivation III

PATHOLOGIC DATA

The time from the onset of symptoms to death varied from two months to two years and eight months, the average being eleven months. Postmortem examinations were performed in all 48 cases. One patient (case 45) died elsewhere, and pathologic material was sent to the clinic by the pathologist who performed the necropsy.

The cases were placed in four groups on the basis of the conditions causing death: cerebral, cardiac, renal and mixed. Seven patients died of cerebrovascular accident, 12 died of cardiac failure. Twenty-three patients died of cardiac and renal failure, 1 died of cerebral accident and renal insufficiency, and 2 died of cerebral, cardiac and renal failure. One patient (case 5) died after an attack which strongly suggested coronary occlusion, but this was not confirmed at necropsy. One patient (case 15) died of massive hemorrhage from a duodenal ulcer. In 1 instance the manner of death of the patient was unknown. In 1 instance the patient was found dead, whether death occurred as a result of cardiac failure or of cerebral accident could not be determined.

In 47 cases the weight of the heart ranged from 390 to 870 Gm, the average being 567 Gm. Hypertrophy of the left ventricle was conspicuous in all cases.

One patient (case 45) was 7 years of age. The heart weighed 180 Gm, and there was marked hypertrophy of the left ventricle, the wall being 24 mm in width at its thickest point. Signs of pericarditis were present in 13 cases. In cases 17, 18, 19 and 41 no exudate was demonstrable, but the pericardial fluid was increased in amount and was cloudy. Clinical signs of pericarditis were confirmed at necropsy in 7 of the 9 cases in which exudate was present. One patient (case 3) had a suggestive pericardial rub prior to death, but no evidence of pericarditis was observed at necropsy.

Aortic sclerosis ranged from mild to severe. In 16 cases sclerosis was mild, in 27, moderate, and in 4, severe. Sclerosis of the coronary arteries was mild in 20 cases, moderate in 20 and severe in 7. Coronary sclerosis could not be demonstrated in case 45.

TABLE 5—*Pathologic Data Forty-Eight Patients Having Diffuse Arteriolar Disease with Hypertension Group 4*

Case	Duration of Life After Onset of Symp toms, Months	Weight of Heart, Gm	Peri carditis, Pathologic	Peri carditis, Clinical	Coro nary Scler osis, Grade	Aortic Scler osis, Grade	Infarction	Com bined Weight of Kidneys, Gm	Arterioles of Myocar dium, Ratio Wall to Lumen	Arterioles of Pectoral Muscle, Ratio Wall to Lumen
1	6	400			1—	1—		270	1 2 06	
2	12	838			3	3+	Patchy, left ventricle	302	1 1 91	
3	8	475		?	1	2		247	1 2 07	
4	2	623	+	+	2	1+		254	1 2 06	
5	8	715			2	2		194	1 1 96	
6	6	496			3	2+		206	1 1 79	
7	3	695			1+	1+		337	1 1 81	
8	8	641	+		1	1		348	1 2 07	
9	4	870			1	2			1 1 82	1 1 36
10	24	540			2	2		285	1 1 96	
11	12	460			1+	2		120	1 1 97	
12	7	474			1	1		233	1 1 97	1 1 13
13	32	618	+	+	2	1		243	1 2 09	1 0 99
14	6	524			2+	2	Patchy, left side of septum		1 1 84	1 1 51
15	4	570		+	3	3+		221	1 1 82	
16	7	465			2	3+		225	1 1 71	
17	13	445	*	+	2	1—		204		1 1 12
18	2	464	*		3	3		218		1 1 15
19	18	630	*		2	2+		248	1 1 99	1 1 36
20	3	486			2	2		305	1 1 93	
21	29**	525	+		2	2+		200	1 1 98	1 1 37
22	24	675			3	1+		385	1 2 11	1 1 25
23	4	471				1—		213	1 2 09	
24	18	564			1+	2		388	1 1 91	
25	24	730	+		1	2		309	1 2 09	
26	4	650			2	2		254	1 2 04	
27	20	534	+	+	1	2+		341	1 1 81	
28	2	632			2	2		216	1 1 97	1 1 98
29	24	565	+	+	1	2		289	1 1 86	
30	21**	390	+		2	1+		200	1 1 81	
31	?	394			2	2		285	1 2 02	1 1 41
32	12	460			2	1+		230	1 1 99	
33	4	722			1	1		270		1 1 36
34	17	727	+		1+	2		346	1 1 94	1 1 41
35	8	405	+	+	1	1+		144	1 1 99	
36	9	651			2	2		324	1 2 04	1 1 18
37	6	656			1+	2		196	1 1 89	1 1 43
38	12	778			1	2+		276	1 1 81	
39	6	519			2	2		280	1 2 14	
40	6	487			3	2		321	1 2 10	
41 †	9	627	*		2+	2+	Septum and anterior portion of left ventricle	366	1 2 12	1 1 44
42	6	554			2+	2+		260	1 1 88	
43 †	18	505	+		2	2+		140	1 1 86	
44	13	530	+	+	1	1		237	1 1 87	1 1 28
45	13**	180			1			130	1 1 72	
46	9	528	+	+	1+	1+		210	1 1 89	1 1 37
47	8	730			2	1+	Patchy, left ventricle	207	1 1 81	1 1 39
48	4	578			1	2	Patchy, septum	326	1 2 02	1 1 23

* No definite exudate but cloudy pericardial fluid

** Patient died at home

† In cases 41 and 43 the anterior descending branch of the left coronary artery was occluded

Occlusion of the coronary arteries occurred in 2 cases (41 and 43), and in both instances the anterior descending branch of the left coronary artery was the vessel affected. In neither case was there a history of coronary occlusion, nor was there electrocardiographic evidence of such an accident. Acute myocardial infarction was demonstrable in the septum and in the anterior apical portion of the left ventricle in case 41. Four patients (cases 2, 14, 47 and 48) had patchy fibrous tissue replacement in the septum, distributed in a manner characteristic of chronic fibrosis of the myocardium.

The combined weight of the kidneys varied from 120 to 388 Gm, the average weight being 256.6 Gm. In only 6 cases was the combined weight of the kidneys less than 200 Gm. Keith, Wagener and Kernohan reported that in their series the kidneys exhibited varying degrees of atrophy but that in most cases the combined weight was only slightly below normal. In all our cases the surfaces of the kidneys presented a granular appearance, with pitting and scarring. The significant pathologic data are given in detailed form in table 5.

HISTOLOGIC STUDIES

Method—Histologic study was made of the myocardium in 45 of the 48 cases in the present series. Material for controls was obtained from 90 patients who did not have hypertension or cardiac enlargement (table 6). No patients were accepted for controls who had a maximal blood pressure exceeding 140 mm of mercury systolic or 90 mm of mercury diastolic. The normal weight of the heart in each case was computed according to the formulas of Smith²⁷. Each patient was selected in such a manner that the actual weight of the heart fell between the minimal and maximal theoretic cardiac weights computed from the theoretic normal body weight of the patient.

Fifteen control subjects were selected for each of the six decades represented in the hypertensive series (table 7). No controls were used for 1 patient (case 45), because she was only 7 years of age. At that age the factor of growth complicates the picture, and it is impossible to establish theoretic normal cardiac weights for the first decade of life.

Sections were cut from the left ventricle, the right ventricle and the interventricular septum. All specimens were fixed in solution of formaldehyde, embedded in paraffin, cut and stained with hematoxylin and eosin, by Van Gieson's method or with elastin H stain. A number of sections were stained according to the Mallory-Heidenhain method.

Particular study was made of the arterioles, i. e., vessels the outside diameter of which was between 25 and 100 microns. This is the criterion

²⁷ Smith, H. L. The Relation of the Weight of the Heart to the Weight of the Body and of the Weight of the Heart to Age, *Am Heart J* 4: 79-93 (Oct) 1928.

for identification of an arteriole used by Kernohan, Anderson and Keith in their study of the arterioles of pectoral muscle

Results—There were moderate but definite changes in the structure of the arteriolar walls in the majority of instances. Moderate thickening of the tunica media, with an increase in the nuclear elements, was seen, however, in no case could the presence of medial fibrosis be demonstrated (fig 1 *A*). In relatively few arterioles evidence of necrosis

TABLE 6—*Mean Wall to Lumen Ratio Arterioles of Pectoral Muscle of Twenty Patients and Arterioles of Myocardium of Forty-Five Patients Having Diffuse Arteriolar Disease with Hypertension, Group 4, Compared with Arterioles of Persons Without Hypertension (Controls)*

Situation of Arterioles Studied	Patients	Hypertension		Patients	No Hypertension	
		Wall to Lumen Ratios (Variations)	Mean Ratio		Wall to Lumen Ratios (Variations)	Mean Ratio
Myocardium	45	1 1 72 to 1 2 02	1 1 95	90	1 2 04 to 1 2 16	1 2 09
Pectoral muscle	20	1 1 14 to 1 1 31	1 1 27	58	1 1 77 to 1 2 72	1 1 97

TABLE 7—*Mean Wall to Lumen Ratios by Decades of Life Arterioles of the Myocardium of Forty-Five Patients Having Diffuse Arteriolar Disease with Hypertension Group 4 and Arterioles of the Myocardium of Ninety Persons Without Hypertension (Controls)*

Age by Decades	Hypertension		No Hypertension	
	Patients	Mean Wall to Lumen Ratio	Patients	Mean Wall to Lumen Ratio
0-9	1	1 1 72		
10-19	0			
20-29	4	1 1 94	15	1 2 05
30-39	8	1 1 96	15	1 2 09
40-49	17	1 2 02	15	1 2 04
50-59	12	1 1 90	15	1 2 16
60-69	2	1 1 82	15	1 2 06
70-79	1	1 1 82	15	1 2 09
Total	45	1 1 95*	90	1 2 09*

* Mean wall to lumen ratio for the entire group in each column

was seen in the tunica media (fig 1 *B*). Some increase in perivascular connective tissue was noted. The elastin H stain disclosed some degree of hypertrophy of the internal elastic lamina, with mild to moderate splitting in most cases (fig 2).

In a number of blood vessels there were apparent mild proliferation of the endothelial cells (fig 3 *A*) and intimal hyperplasia, however, in only a few cases was there intimal thickening sufficient to be significant (fig 1 *B*). Partial occlusion of the arteriolar lumen was noted in a few instances, but in none was the lumen completely occluded.

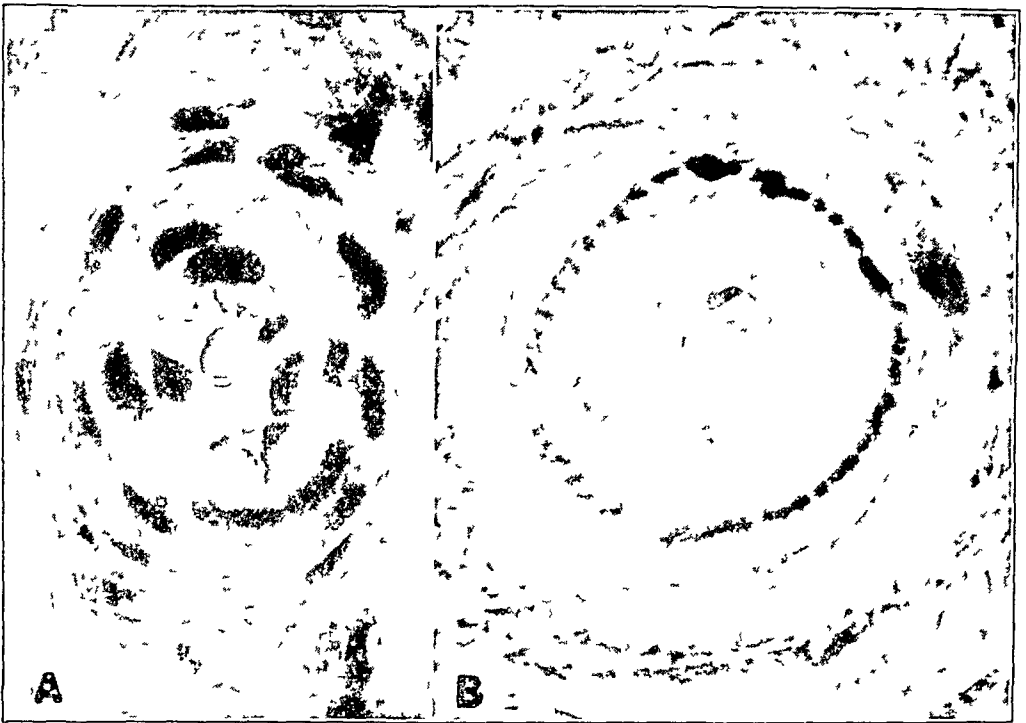


Fig 1—*A*, section of an arteriole (case 47) Thickening of the wall is evident, and the medial nuclei are increased in number Hematoxylin and eosin, $\times 850$ *B*, section of an arteriole (case 11), showing an extreme degree of intimal thickening, with almost complete obliteration of the lumen, evidence of medial necrosis can be noted Elastin H, $\times 735$

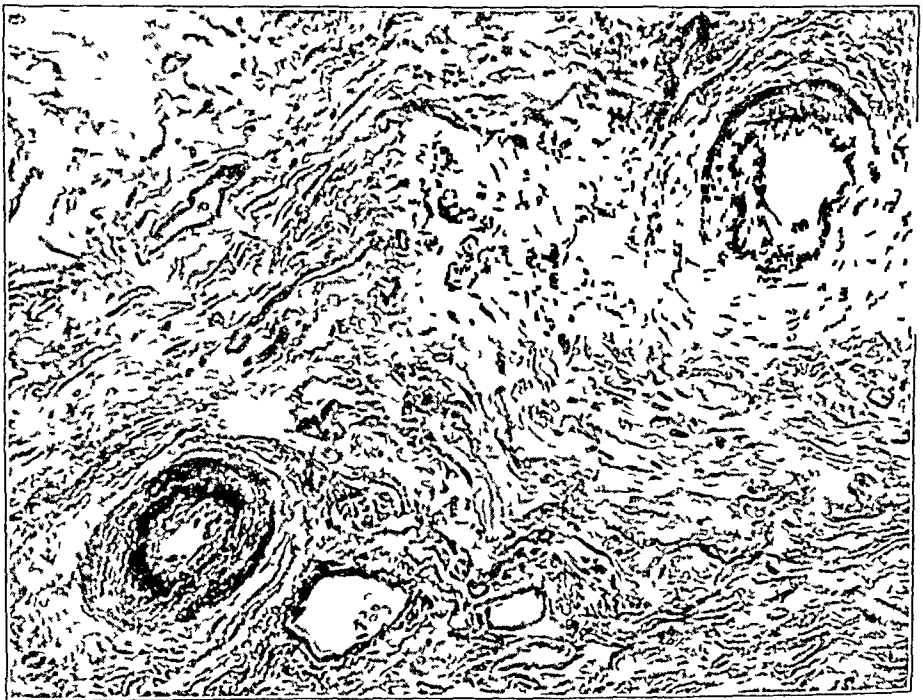


Fig 2 (case 43) —Section of arterioles Hypertrophy of the internal elastic lamina can be noted in the lower vessel, and intimal thickening is conspicuous in both vessels Elastin H, $\times 180$

One of the most striking features was the relative frequency with which fibrous tissue replacement in the myocardium occurred in the hypertensive group as compared with the nonhypertensive group, irrespective of the age of the patient or the degree of coronary arteriosclerosis present (fig 3 *B*). Varying degrees of fibrosis, ranging from mild to moderate, occurred in several of the nonhypertensive patients, but in general there was a definite increase of fibrosis in the myocardiums of hypertensive patients compared with that in the myocardium of nonhypertensive patients.

The most noticeable observation was the lack of consistency of the structural changes in the arterioles. Not only was there a wide variation

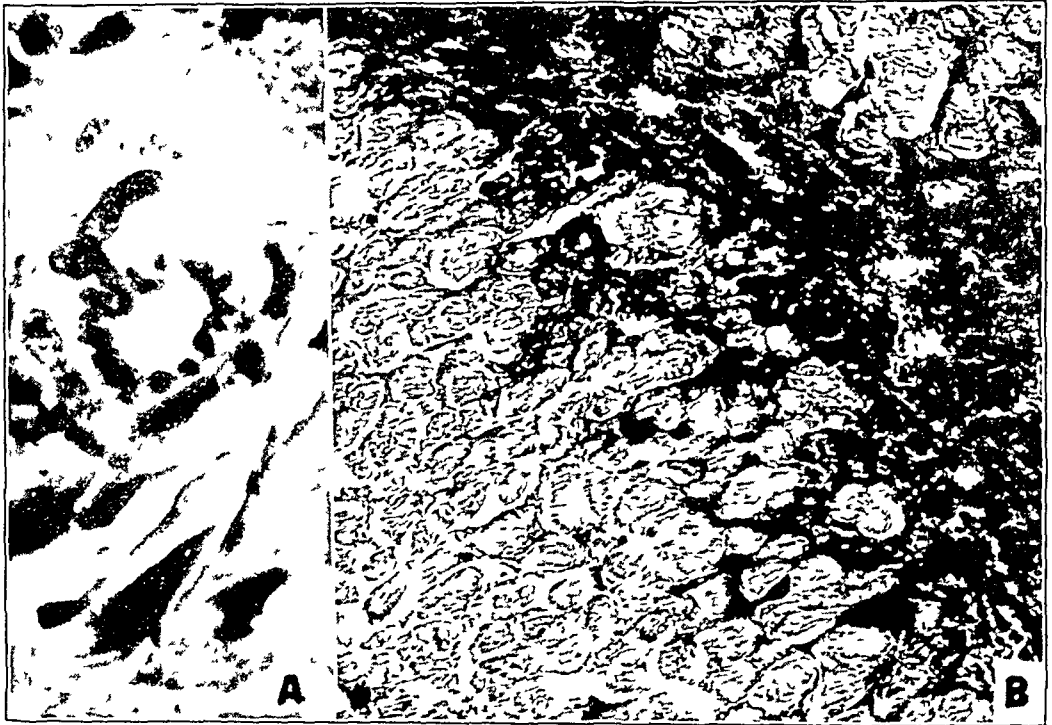


Fig 3—*A*, section of an arteriole (case 45) showing apparent mild proliferation of endothelial cells. Van Gieson, $\times 860$. *B*, extensive diffuse myofibrosis in the myocardium (case 9). Van Gieson, $\times 195$.

in the findings from case to case, but there was a striking variation among the different arterioles in the same case and in different segments of the same arteriole (fig 4).

The outside and inside diameters of the myocardial arterioles were measured in all cases, and the wall to lumen ratios were computed. This was done after the method described by Kernohan, Anderson and Keith, and a Bausch and Lomb micrometer was used. Estimations were made on six arterioles in each case, and the mean wall to lumen ratio was computed. Only those vessels which were cut in cross section were considered suitable for measurement.

It was found that in the series of nonhypertensive patients the mean wall to lumen ratio for arterioles of the myocardium was 1.209, with

variations from 1.204 to 1.216. In the series of cases of malignant hypertension the mean ratio was 1.195, with variations from 1.172 to 1.202 (table 6). There was no significant relation between the mean wall to lumen ratio and the age of the patient in either the normal or the hypertensive group (table 7). It should be stated that it was impossible to distinguish on the basis of the wall to lumen ratio between nonhypertensive patients and patients with malignant hypertension.

Figures 5 and 6 show these results in graphic form. In figure 5 the mean wall to lumen ratios are plotted as abscissas against the percentile frequencies as ordinates. It is apparent that there is con-

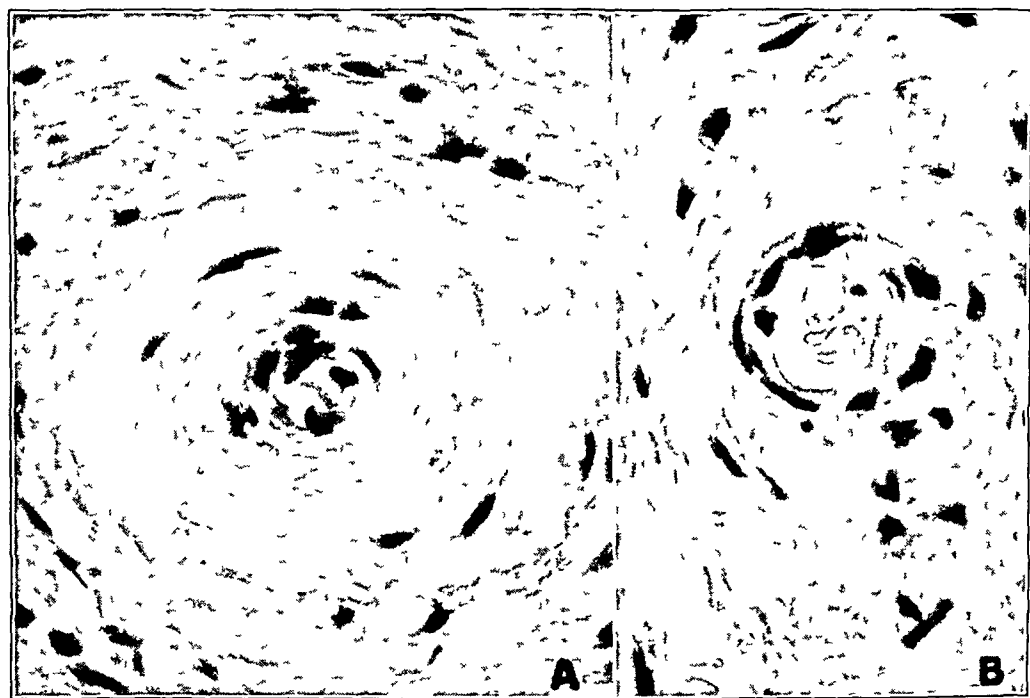


Fig 4 (case 43).—Marked segmental distribution of arteriolar changes in the myocardium. *A*, section of an arteriole. The apparent marked thickening of the wall of the vessel is the result of increase in perivascular connective tissue. Hematoxylin and eosin, $\times 605$. *B*, same vessel shown in *A*, with several sections removed. Van Gieson, $\times 605$.

siderable overlapping between the mean wall to lumen ratios for arterioles of the nonhypertensive patients and those for arterioles of the hypertensive group, especially when the ratio falls between 1.18 and 1.21.

In figure 6 the widths of the arteriolar lumens in microns have been plotted as abscissas against the mean thicknesses of the arteriolar wall as ordinates. Each point represents the mean thickness of the wall of all vessels having the same width of lumen. Lines were drawn through these points to indicate the mean about which the values for hypertensive and those for the nonhypertensive arterioles are arranged. Because the angle formed by this line and the ordinate represents the mean wall to lumen ratio, it is apparent that the nearer this line

approaches the ordinate, the smaller is the mean wall to lumen ratio. It follows that the greater the total diameter of the arteriole, the greater is the difference in mean ratio between the hypertensive and the non-hypertensive arterioles

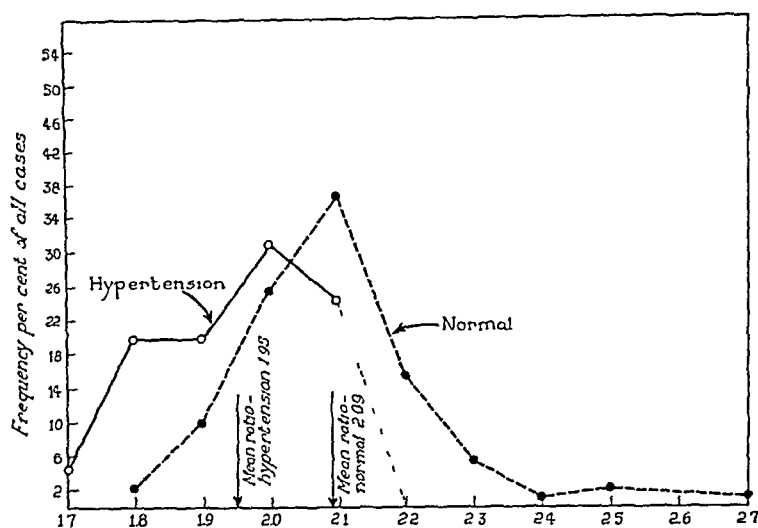


Fig 5—Percentile frequency distribution and wall to lumen ratio for the arterioles of the myocardium (patients with malignant hypertension and persons without hypertension)

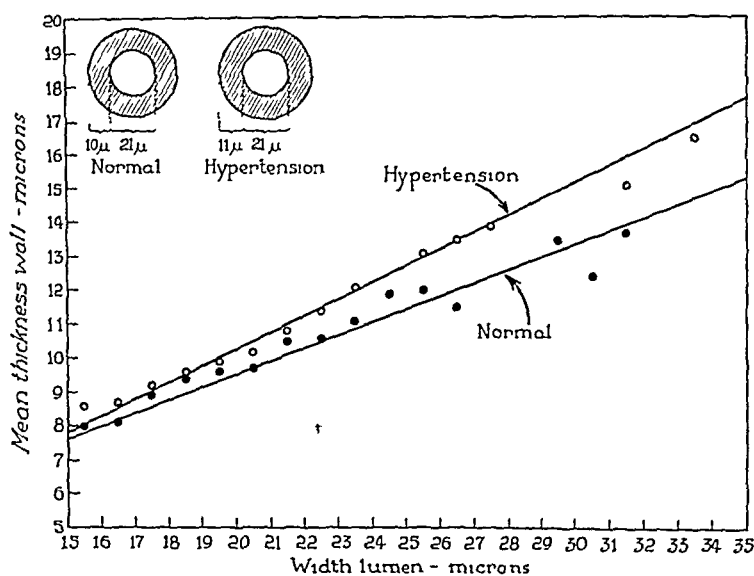


Fig 6—Thickness of the wall and width of the lumen in the arterioles of the myocardium (patients with malignant hypertension and persons without hypertension)

The diagrams in the upper left hand corner of figure 6 represent mean measurements of the diameters of the wall and lumen of the entire series, for both the hypertensive and the nonhypertensive group

As a comparative study, the wall to lumen ratios of the arterioles of pectoral muscle were computed for 20 of the 45 patients with malignant hypertension and for 58 nonhypertensive patients. The mean wall to

lumen ratio of control subjects was 1.197, which compares favorably with Kernohan's²¹ figure of 1.20. In the hypertensive group the mean wall to lumen ratio was 1.127 (table 6). The pathologic changes in

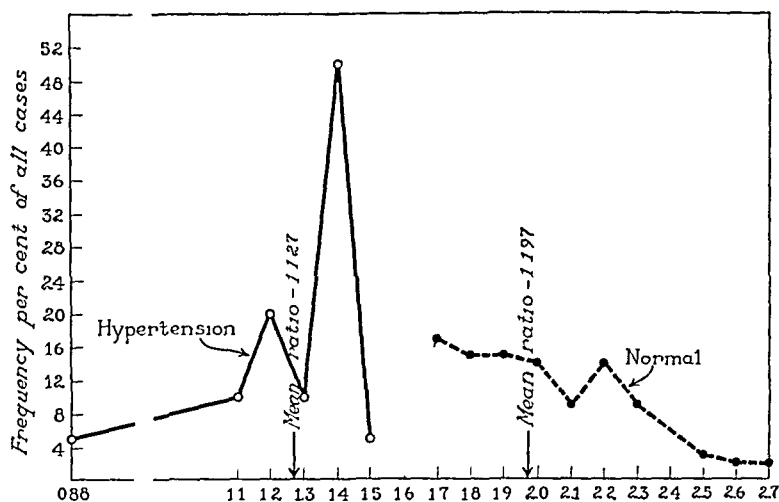


Fig 7—Percentile frequency distribution and wall to lumen ratios for arterioles of pectoral muscle (patients with malignant hypertension and normal persons)

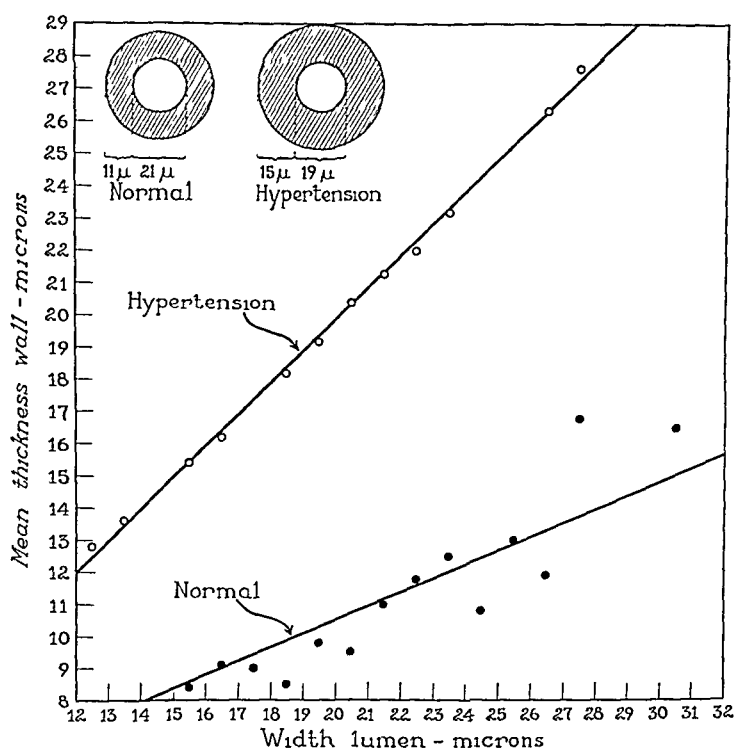


Fig 8—Thickness of the wall and width of the lumen in arterioles of the pectoral muscle (patients with malignant hypertension and normal persons)

the arterioles themselves were similar to those described by Kernohan, Anderson and Keith. This comparison emphasizes the fact that arteriolar changes do occur in the myocardium in the presence of malignant hyper-

tension, although they are less marked than in skeletal muscle and other organs

Figures 7 and 8 have been constructed in the same manner as figures 5 and 6 and represent the relation between the arterioles of the pectoral muscle in the hypertensive group and those in the nonhypertensive group

COMMENT

The results of this study indicate that in the presence of diffuse arteriolar disease with hypertension group 4, structural changes in varying degrees of severity occur in the arterioles of the myocardium. The exact nature of these changes has been a subject for considerable controversy during the years since Bright first suggested the existence of a relation between vascular changes and cardiorenal disease. Johnson's original belief that changes in the tunica media are essentially proliferative has been substantiated by Ewald, Fischer and Schlayer,²⁸ Brogsitter,²⁹ Evans,³⁰ Kernohan and his associates, Moritz and Oldt, Pilcher and Schwab and others. The belief that the changes are degenerative finds support in the work of Gull and Sutton, Jores, Fishbein and others.

In the foregoing study, wide variation from case to case was noted in the nature and degree of change. Increase in the medial nuclei seemed to be an early change, with hyperplasia of the internal elastic lamina, intimal proliferation and degenerative changes occurring later in the process. It is a significant fact that structural changes in the myocardial arterioles were not observed in all cases and that, when they did occur, the changes were similar to those occurring in other organs in the same case, although less pronounced.

The analysis of the clinical features in this series of cases substantiates the statement of Keith and his co-workers¹ that the syndrome of malignant hypertension is a clearcut clinical entity and that the clinical picture may be characterized by symptoms predominantly cerebral, cardiac or renal or by any combination of the three. This conception is in accordance with the conclusion of Gull and Sutton that the clinical history varies from case to case according to the organ or organs most severely affected.

The presence of diffuse fibrosis in the myocardium in increased degree among the hypertensive patients is in accordance with the

28 Fischer, H., and Schlayer. Arteriosklerose und Fühlbarkeit der Arterienwand, *Deutsches Arch f klin Med* **98** 164-185, 1910.

29 Brogsitter, A. M. Zur Anatomie der Splanchnikusgefasse beim Hochdruck, *Munchen med Wchnschr* **2** 1049-1051 (Aug 1) 1924.

30 Evans, G. A Contribution to the Study of Arterio-Sclerosis, with Special Reference to Its Relation to Chronic Renal Disease, *Quart J Med* **14** 215-282 (April) 1921.

observations of Fahr,³¹ who explained this phenomenon on the basis of hypertrophy of the cardiac musculature and insufficient circulation and supply of oxygen to the hypertrophied muscle cells, with resultant necrosis and fibrosis

Not only was there wide variation in the occurrence and degree of severity of the histologic changes among individual patients, but there was a striking difference in the degree of involvement between different vessels of the same patient and between different segments of the same vessel. Moritz and Oldt observed similar segmental distribution in their study of the pathologic changes occurring in the arterioles of skeletal muscle of hypertensive patients.

From the evidence presented here and from data collected by others, it appears that malignant hypertension is a diffuse arteriolar disease in every sense of the term and that no organ which is subjected to elevation in systemic blood pressure can escape entirely. Why structural changes in the arterioles of the myocardium do not progress at the same rate or to the same degree as do similar changes in the arterioles of other organs is a question which has yet to be answered.

31 Fahr, G. The Heart in Hypertension, *J. A. M. A.* **105** 1396-1400 (Nov. 2) 1935.

FATTY DEGENERATION OF THE HEART CAUSING MYOCARDIAL INSUFFICIENCY

REPORT OF A CASE

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Fatty degeneration of the heart is a retrogressive condition in which fat droplets are found in the myocardial sarcoplasm. It is usually secondary to such conditions as myocarditis, pericarditis, coronary arteriosclerosis, myocardial insufficiency, starvation, anemia, fever, phosphorus or arsenic poisoning, diphtheria, scarlet fever, typhoid fever and various other diseases but has been noted to occur without any demonstrable cause¹. The condition is common, especially in minor degrees.

Concerning the functional significance of fatty degeneration of the heart there is no unanimity of opinion. Lewis² stated "Fatty heart should not be diagnosed. In severe diphtheria the cardiac muscle may be so degenerate with fatty particles that it is throughout of a pure yellow colour, yet the heart continues beating. Because diffuse fatty degeneration occurs in the senile heart, or in coronary artery disease, that is no reason for regarding fat in the heart as a cause of sudden death. Equal change is found in the heart of pernicious anaemia and here sudden death is most unusual."

Willius³ stated "Fatty degeneration does not produce cardiac insufficiency." MacCallum⁴ wrote that "the presence of fatty degeneration seems to have very little detrimental effect upon the function of the heart." Herrmann⁵ concluded that fatty degeneration occurring during the course of infections is "rarely sufficient to produce heart failure." Welch,⁶ in studying animals kept for a long time at fever heat, found

From the Department of Medicine of Cleveland City Hospital and the School of Medicine of Western Reserve University

1 Delafield, F, and Prudden, T M. A Text-Book of Pathology, ed 15, New York, William Wood & Company, 1931, pp 619-620

2 Lewis, T. Diseases of the Heart, ed 2, New York, The Macmillan Company, 1937, p 250

3 Willius, F A. The Heart in Obesity, Mod Concepts Cardiovasc Dis, 1938, vol 7, no 9

4 MacCallum, W G. A Text-Book of Pathology, ed 6, Philadelphia, W B Saunders Company, 1936, p 452

5 Herrmann, G R. Synopsis of Diseases of the Heart and Arteries, St Louis, C V Mosby Company, 1936, p 170

6 Welch, cited by MacCallum⁴

abundant deposition of fat in their hearts but no special functional alteration

On the other hand, Delafield and Prudden¹ noted that fatty degeneration of the heart may "lead to thinning of the walls, or to rupture of the heart, or to inability to fulfil its functions" and that "it is not infrequently a cause of sudden death" Muir⁷ stated that the importance of fatty degeneration has been "much exaggerated," even though "the reserve power is diminished and the heart may suddenly fail"

Monckeberg⁸ went so far as to state that fatty degeneration of the myocardium cannot be regarded as an unimportant lesion of the heart muscle, and that it may be cited as one of the causes of the development of heart failure No specific cases were described

This communication reports a case of chronic congestive heart failure in which autopsy revealed no explanation for the myocardial insufficiency except severe idiopathic fatty degeneration of the myocardium Search of the literature has revealed no comparable case

REPORT OF CASE

C D, a white man aged 42, an office worker, who entered the Cleveland City Hospital Dec 5, 1938, had been in excellent health until October 1937, when he first noted shortness of breath, weakness and edema of the ankles Despite treatment, the symptoms became more marked, and in April 1938 he was forced to go to bed, where he remained until July At this time he was sufficiently improved to return to work The shortness of breath and edema returned, however, and became increasingly severe, so that he was admitted to the hospital There was no history of any sort of pain in the chest or of hypertension The diet had been adequate and well balanced

The patient's past and marital histories were not remarkable He had never had scarlet fever, chorea, rheumatic fever or venereal disease He was married and had two healthy children

On physical examination the patient was found to be suffering from severe myocardial insufficiency He was markedly dyspneic, edematous from the chest down and cyanotic The veins of the neck were distended The heart was considerably enlarged There was gallop rhythm, the cardiac mechanism was normal and the rate was 120 beats per minute There were rales at the bases of the lungs The liver was enlarged and tender The eyegrounds were normal The blood pressure in millimeters of mercury was 110 systolic and 85 diastolic, and the temperature was 38 C

Urinalysis revealed albumin, grade 3, and a specific gravity of 1.032 During the course in the hospital the albumin disappeared from the urine The erythrocytes numbered 5,240,000 per cubic millimeter and the leukocytes 9,250 and the value for hemoglobin was 105 per cent The Kline test for syphilis gave a negative result The urea nitrogen content was 27.3 mg per hundred cubic centimeters of blood Fluoroscopic and roentgen studies of the heart and aorta showed

⁷ Muir, R Text-Book of Pathology, Philadelphia, J B Lippincott Company, 1924, p 263

⁸ Monckeberg, J G Die Erkrankungen des Myokards und des spezifischen Muskelsystems, in Henke, F, and Lubarsch, O Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1924, vol 2, pt 3, p 345

the heart to be greatly enlarged in all directions and to have pulsations of very small amplitude. The electrocardiogram showed low voltage in all leads and an inverted T wave in leads II and III.

Despite treatment, the patient remained in marked congestive heart failure and was critically ill. He had a right pleural effusion which required aspiration three times. There were several episodes suggesting pulmonary infarction. The temperature varied between 37 and 41 C, the pulse rate between 90 and 140



Photomicrograph (scarlet red fat stain) showing the innumerable fine droplets of fat in the myocardial fibers. This section shows an area in which the involvement was relatively moderate. In many areas the droplets of fat were confluent. $\times 276$

beats per minute and the blood pressure between 84 and 122 systolic and 60 and 96 diastolic. The patient died December 26.

The initial clinical diagnosis was sclerosis of the coronary arteries with myocardial fibrosis and heart failure, but this was changed to acute isolated (Fiedler's) myocarditis shortly before death.

Autopsy Observations (Dr. L. L. Terry) —There was ample evidence of chronic myocardial insufficiency in the form of severe passive hyperemia of the viscera,

hydrothorax (on the right), edema of the legs and dilatation of the heart. There were recent infarcts in the lower lobes of both lungs and thrombi in the branches of the pulmonary artery to the right lung.

The heart weighed 405 Gm. It was remarkably soft and flabby. When placed on a flat surface it quickly flattened out into a shapeless mass. The myocardium was a peculiar pale brownish yellow. There were numerous small mural thrombi in the left ventricle. Otherwise the heart showed no abnormalities. The epicardium, endocardium, valves and coronary arteries were completely normal. The amount of subepicardial fat was slightly less than usual. The remaining viscera showed no significant changes other than hyperemia.

Microscopic examination of numerous sections from the heart showed the endocardium and epicardium to be normal. The myocardial fibers were large, pale, granular, vacuolated and severely fragmented, and the cross striations were obscure. The nuclei showed considerable variations in size, shape and staining affinities. There was no evidence of inflammation and no fibrosis, and the large and small arteries were normal.

Fat stain showed the myocardial fibers uniformly to contain innumerable fine droplets of fat (see accompanying illustration). In certain areas the droplets were arranged in longitudinal lines, in others the droplets were so abundant as to be confluent.

Microscopic examination of the other viscera confirmed the diagnoses made on gross examination. In addition, the liver showed fatty metamorphosis of slight degree. There was no arteriolar nephrosclerosis. The skeletal muscle fibers showed no abnormalities.

COMMENT

From a clinical standpoint it was clear that the patient in this case suffered from severe chronic myocardial insufficiency, but the cause of the heart failure was not apparent. Coronary arteriosclerosis without thrombosis or angina pectoris but with diffuse myocardial fibrosis could not be excluded and statistically is the most probable of the several possible causes of heart failure of obscure cause. The appearance of fever suggested the possibility of Fiedler's myocarditis, although it was realized that the elevated temperature could be due to pulmonary infarction.

The fatty degeneration discovered at autopsy was so severe, however, as to leave little doubt that it was the cause of the myocardial insufficiency. The muscle fibers were virtually full of fat, and there were severe degenerative changes involving the nuclei. The cause of this degeneration could not be ascertained. Such factors as inadequate diet, blood dyscrasias, chronic disease and infection could be eliminated. That the myocardial insufficiency itself could have produced such marked changes is contrary to all experience. Furthermore, such reasoning would leave one without an explanation as to why the heart failed in the first place.

CONCLUSION

Severe idiopathic fatty degeneration of the myocardium must be considered as an etiologic possibility in cases of heart failure of obscure origin.

DIABETES INSIPIDUS ASSOCIATED WITH DIABETES MELLITUS

METABOLIC STUDIES AND REPORT OF A CASE

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W V CONSOLAZIO, B S

AND

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The development of glycosuria in a patient with diabetes insipidus is not unique and frequently accompanies this metabolic disorder¹ The coexistence of frank diabetes mellitus and diabetes insipidus, on the other hand, is rare, and less than 25 case reports on patients with both dyscrasias² have been recorded in the available literature Overlapping of signs and symptoms and the possible existence of at least two types of each disease have rendered the confirmation of both diagnoses difficult Recent advances in the technic of study and interpretation of metabolic disorders have been of great help, however, and it is believed that the data to be presented satisfy the criteria for the diagnosis of diabetes insipidus and of diabetes mellitus

The patient who will be discussed in this communication was under observation intermittently for more than eighteen months On three occasions during this time she was admitted for observation to the

Aided by the Corn Industries Research Foundation

From the Medical Clinic of the Massachusetts General Hospital and the Fatigue Laboratory of Harvard University

1 (a) Evans, G, and Wallis, R L M Diabetes Insipidus Complicated by Intermittent Glycosuria, *Lancet* **1** 70, 1921 (b) Rabinowitch, I M Metabolic Studies on a Case of Diabetes Insipidus, *Arch Int Med* **28** 355 (Sept) 1921 (c) Gibson, R G, Magers, E J, and Dulaney, H Blood Sugar Curves in Diabetes Insipidus and in Habitual and Experimental Excessive Water Drinking, *Endocrinology* **11** 341, 1927 (d) Lewin, C Zur Frage des Zusammenhangs des Diabetes mellitus und Diabetes insipidus, *Med Klin* **15** 133, 1919

2 (a) Greene, J A, and Gibson, R B Coexistence of Diabetes Mellitus and Diabetes Insipidus Report of a Case with Pregnancy, *J Lab & Clin Med* **24** 455, 1939 (b) Senator, H Ueber die Beziehungen zwischen Diabetes mellitus und insipidus, *Deutsche med Wchnschr* **24** 385, 1897 (c) Allan, F N, and Rowntree, L G The Association of Diabetes Insipidus and Diabetes Mellitus, *Endocrinology* **15** 97, 1931

metabolism ward of the Massachusetts General Hospital After the completion of certain routine procedures, an investigation of the constituents of body fluids, electrolyte exchange and renal function in the diabetes insipidus syndrome was pursued No attempt will be made to survey the literature on diabetes insipidus Several comprehensive reviews³ have appeared in recent years, which do justice to the syndrome and its various manifestations

METABOLIC REGIMEN AND LABORATORY METHODS

During most of her stay in the hospital the patient consumed a constant diet which contained 140 Gm of carbohydrate, 62 Gm of protein and 49 Gm of fat The difference between the weight of the freshly prepared diet and that of the same diet after desiccation was approximately 480 Gm This refers to water in the food, it is not included in the columns on fluid intake in the tables The intake of fluids was 4,000 cc per day except when stated otherwise Under this regimen the urine contained less than 0.1 Gm of reducing substances daily Preparation of the food, collection of excreta⁴ and the methods used for analysis of the various constituents of the blood, the urine, the diet and the stool have been described⁵ Plasma volume was determined according to the method described by Gibson and Evans⁶ Interstitial fluid volume was determined according to the method of Crandall and Anderson⁷ Inulin and creatinine clearances were determined according to the method of Shannon and Smith⁸ Sodium, chloride and potassium clearances were calculated by the same formula as inulin clearance

3 (a) Peters, J. P. *Body Water: The Exchange of Fluids in Man*, Springfield, Ill., Charles C. Thomas, Publisher, 1935 (b) Fisher, C., Ingram, W. R. and Ranson, S. W. *Diabetes Insipidus and the Neuro-Hormonal Control of Water Balance*, Ann Arbor, Mich., Edwards Brothers, Inc., 1938 (c) Bellows, R. T., and Van Wagenen, W. P. *The Relationship of Polydipsia and Polyuria in Diabetes Insipidus: A Study of Experimental Diabetes Insipidus in Dogs With and Without Esophageal Fistulae*, *J. Nerv. & Ment. Dis.* **88**: 417, 1938

4 Talbott, J. H., Jacobson, B. M., and Oberg, S. A. *The Electrolyte Balance in Acute Gout*, *J. Clin. Investigation* **14**: 411, 1935

5 Talbott, J. H. *Interpretation of Clinical Chemical Procedures*, Ohio State M. J. **35**: 137, 1939

6 Gibson, J. G., Jr., and Evans, W. A., Jr. *Clinical Studies of Blood Volume. I. Clinical Application of a Method Employing Azo Dye "Evans Blue" and the Spectrophotometer*, *J. Clin. Investigation* **16**: 301, 1937

7 Crandall, L. A., Jr., and Anderson, M. X. *Estimation of the State of Hydration of the Body by the Amount of Water Available for the Solution of Sodium Thiocyanate*, *Am. J. Digest. Dis. & Nutrition* **1**: 126, 1934

8 Shannon, J. A., and Smith, H. W. *The Excretion of Inulin, Xylose and Urea by Normal and Phlorizinized Man*, *J. Clin. Investigation* **14**: 393, 1935

REPORT OF CASE

O F, a white American-born housewife aged 46, was admitted to the Massachusetts General Hospital on Nov 17, 1937, complaining of polyuria, polydipsia and pruritus vulvae

Family History—One sister was known to have diabetes mellitus. There were no other hereditary or congenital stigmas in the family.

Past History—As a child the patient had intermittent severe headaches and nocturia (two to three times) each night. There was no history of trauma to the head or of any sickness which suggested encephalitis. During twenty-two years of married life she had been pregnant five times. She had three living children. The oldest child was treated for pulmonary tuberculosis in a sanatorium in 1929. Menstruation stopped at the age of 33, after the birth of her fifth child. Hot flashes appeared and persisted for more than a year. The early development of the menopause was not explained satisfactorily. In 1926 her weight was 230 pounds (104 Kg). In 1936, it was 205 pounds (93 Kg). On admission to the hospital it was 190 pounds (86 Kg).

Present Illness—The present illness began in 1932. Polyuria, polydipsia and severe headaches were the principal complaints. Medical advice was sought, and on a routine examination of the urine dextrose was found. A diagnosis of diabetes mellitus was made, and injections of insulin were recommended. These were taken daily for more than two years, with considerable subjective improvement. In 1934 the daily output of urine appeared to be increasing, and another physician was consulted. Examination of the urine at that time showed no reducing substances, while the low specific gravity suggested that another type of diabetes was present. The patient was advised to discontinue insulin, reduce her sodium chloride intake and take 1 cc of solution of posterior pituitary U S P parenterally daily. This advice was followed for more than two years, with partial alleviation of symptoms. In 1935 the location of her headaches changed from the top of her head to the temporal regions, and the incidence increased to at least once every twenty-four hours. Impairment of vision for near and distant objects was noted for the first time.

Two months before admission polydipsia and polyuria became more severe and a new symptom, pruritus vulvae, was noted. Glycosuria was rediscovered, and a determination of the value for "fasting blood sugar" showed the concentration to be 250 mg per hundred cubic centimeters. She was referred to the hospital with the presumptive diagnosis of diabetes insipidus and diabetes mellitus.

Physical Examination—Examination in the ward showed the patient to be well developed and moderately obese. The face was florid. All of the teeth had been removed. The vaginal mucous membrane was atrophied, and the uterus was slightly enlarged. The blood pressure was 150 systolic and 82 diastolic.

A neurologic examination by Dr G C Caner gave negative results.

An examination of the eyes by Dr E B Dunphy showed the visual acuity to be 20/40 in both eyes, with normal fundi and normal visual fields.

Partial Laboratory Data—The specific gravity of the urine was 1.004. It contained about 0.1 per cent reducing substances but no albumin, ketone bodies, blood cells or casts. The Hinton reaction of the blood was negative. The concentration of serum cholesterol was 178 mg per hundred cubic centimeters. An electrocardiogram was interpreted as normal. The roentgen ray films were interpreted by Dr Richard Schatzski as follows: "Lateral and anterior-posterior views of the skull show slight elevation of the posterior clinoid processes without evidence of destruction. There is calcification of the dura near the longitudinal sinus

The convoluted markings are increased The findings are suggestive of a small tumor in the region of the pituitary body The bones of the hands and feet appear normal"

A lumbar puncture showed normal dynamics The fluid contained 19 mg of protein per hundred cubic centimeters No white or red blood cells were seen The colloidal gold curve was 0000000000 The basal metabolic rate was determined on two occasions by the Tissot gasometer method On December 9 it was +9 per cent, and the respiratory quotient was 0.74 On December 21 it was -1 per cent, and the respiratory quotient was 0.76 The rate of excretion of 60 mg of phenolsulfonphthalein injected intravenously was 28 per cent in fifteen minutes and a total of 66 per cent in two hours Other laboratory data are given in the tables

Course—Various experimental studies were done during each stay in the hospital These will be discussed in detail During the first stay an attempt was made to relieve the polydipsia, a most distressing symptom Rinsing the mouth with cold water, sucking ice and a low sodium chloride intake proved to be effective On the control diet, glycosuria was minimal and pruritus vulvae disappeared

Readmission was advised for further study two months after discharge The patient believed that her symptoms had improved in the interim Thirst was less distressing, and it was necessary to void urine only once each night The urine was tested for reducing substances several times a week All tests gave negative results She remained in the hospital one month

The third admission occurred on Oct 17, 1938 This was considered expedient in order to repeat certain experimental studies and to investigate the failing vision The results of physical examination were unchanged except for the eyes, both of which showed cataracts After completion of the experimental studies in the metabolism ward she was transferred to the Massachusetts Eye and Ear Infirmary, on November 30 Extraction of an intracapsular cataract from the left eye was successful, and recovery was uneventful

Because of inability to control the severe headaches and the possibility of an expanding tumor of the pituitary a trial course of roentgen therapy was recommended This consisted of 300 r daily to the region of the pituitary for six days A 4 by 5 cm field was used at a distance of 50 cm Partial alleviation of headaches was achieved The roentgen treatments were repeated, therefore, in May 1939 The same dosage, field and distance were employed The patient was seen last in October She believed that her general condition was better than at any time for more than three years All of the previously distressing symptoms were alleviated She continued with the same diet which had been prescribed at the first admission

METABOLIC STUDIES

The data in support of a diagnosis of diabetes mellitus were convincing The family history of diabetes mellitus, polyuria, polydipsia, glycosuria and pruritus vulvae, as well as the symptomatic relief after administration of insulin, was presumptive evidence The sugar tolerance studies⁹ confirmed this impression (table 1) The value for "fasting whole blood sugar" before each of three tests varied between 204 and 220 mg per hundred cubic centimeters An elevation of the level of blood sugar similar to that seen in patients with diabetes mellitus

9 Lindeboom, G A Beobachtungen bei einem Fall von Diabetes insipidus et mellitus, *Deutsches Arch f klin Med* **175** 74, 1933

followed ingestion of 100 Gm each of dextrose, galactose and levulose. Two hours after ingestion of dextrose the concentration of blood sugar increased to 440 mg per hundred cubic centimeters. The concentration of reducing substances in the urine collected at the same time was about 2.0 Gm per hundred cubic centimeters. Ninety minutes after ingestion of galactose the concentration of blood sugar increased to 396 mg per hundred cubic centimeters. Approximately 1.0 Gm of reducing substances per hundred cubic centimeters was excreted in the urine. After the ingestion of levulose the concentration of blood sugar increased to a maximum of 276 mg per hundred cubic centimeters. Acetone bodies in the urine were never observed by us. Since the prescribed diet in the hospital was sufficiently low in carbohydrate to prevent glycosuria, acetonuria from uncontrolled diabetes mellitus was not anticipated.

Our next interest was in confirmation of the diagnosis of diabetes insipidus and the study of several of its manifestations. Polydipsia, polyuria and headaches may be presenting symptoms of diabetes insipidus, as well as of diabetes mellitus. A low specific gravity of the urine and an increased concentration of serum sodium are significant laboratory findings. Presumptive exclusion of other dyscrasias completes the argument.

TABLE 1—*Experimental Observations on Blood and Urine After Ingestion of 100 Gm Each of Dextrose, Galactose and Levulose*

Time, Minutes	Dextrose		Galactose		Levulose	
	Blood Sugar, Mg per 100 Cc	Urine Sugar, Gm per 100 Cc	Blood Sugar, Mg per 100 Cc	Urine Sugar, Gm per 100 Cc	Blood Sugar, Mg per 100 Cc	Urine Sugar, Gm per 100 Cc
0	220	0.0	218	0.0	204	0.0
30	332		320		246	
60	384	0.5	344	1.0	276	0.1
90	408		396		254	
120	440	2.0	346	1.0	234	0.1
150	336		272		216	
180	300	2.0	252	1.0	194	0.0

The daily water exchange varied from 4 to 8 liters. This is not excessive for a patient with diabetes insipidus and is less than that reported by some observers. Thirst, however, was persistent and insatiable. We believe that greater diagnostic significance should be given to the severity of thirst than to the absolute amount of fluid exchange. In cases of psychogenic polyuria, increased ingestion of fluid becomes habitual, and the output of urine may exceed 5 liters a day. Thirst is not insatiable, however, and restriction of fluids is not accompanied by distressing symptoms as it is in patients with diabetes insipidus.

A sustained low specific gravity of the urine is unusual in any disease except diabetes insipidus and advanced renal failure. Most routine specimens collected from this patient had a specific gravity below 1.006. The maximum specific gravity after thirty hours' abstinence from fluid was only 1.011. It was necessary to give solution of posterior pituitary¹⁰ to increase the specific gravity above 1.020.

Appreciation of the significance of elevated values for serum sodium and total fixed base in diabetes insipidus is recent. It is believed, however, that they are of

10 Christie, C. D., and Stewart, G. N. Study of a Case of Diabetes Insipidus with Special Reference to the Mechanism of the Diuresis and of the Action of the Pituitary Extract on It, *Arch Int Med* 20:10 (July) 1917.

great diagnostic help About twenty years ago, Veil¹¹ and later Meyer and Meyer-Bisch¹² advanced the hypothesis that there are two kinds of diabetes insipidus, a hyperchloremic and a hypochloremic type No satisfactory method for determination of the level of serum sodium was available at that time It is likely that the terms "hypernatremic" and "hyponatremic" would have been used if sodium methods had been available, since the concentration of serum "sodium" is a better index of the concentration of sodium chloride than is the concentration of serum "chloride" Butler and his associates¹³ were the first to study the increased concentration of serum sodium in diabetes insipidus and found that hyperchloremia is accompanied by hypernatremia

The data in this communication confirm these observations On the morning of Nov 23, 1937, the concentration of serum sodium was 144.9 milliequivalents, and the concentration of total fixed base was 157.1 milliequivalents, per liter (table 2) These values are above the average range for normal persons (sodium, 139 to 141 milliequivalents, and total base, 150 to 155 milliequivalents, per liter) as determined in our laboratory⁵ It should be reiterated that during the week before this sample of blood was obtained the daily intake of fluid was 4,000 cc This represented, probably, a restriction in the amount which would have been consumed had fluid been allowed ad libitum The output of urine under this regimen was approximately 3,000 cc daily After collection of the first sample of blood the extradietary fluid intake was restricted to 100 cc in twenty-four hours All of the diet was consumed In the twenty-four hour period the body weight diminished 1.8 Kg The output of urine decreased 1,500 cc Intense thirst was present, but chemical evidence of dehydration was lacking in the sample of blood taken on November 24 The oxygen capacity and cell volume had increased slightly, but the value for serum protein decreased from 6.8 to 6.5 Gm per hundred cubic centimeters The total fixed base, however, increased to 164.3 milliequivalents, that for sodium to 151.6 milliequivalents and that for chloride to 109.5 milliequivalents per liter, respectively The increased concentrations of these constituents are believed to be significant and have been interpreted by us as confirmatory evidence of diabetes insipidus

After relative abstinence from fluid for one day, amounts of 9,500 cc and 7,500 cc respectively were given in the subsequent twenty-four hour periods The output of urine was 5,900 cc for one period and 7,300 cc for the other A gain in weight of 0.8 Kg was observed A third sample of blood was taken on November 26 The concentrations of total fixed base, sodium and protein were similar to those observed in the first sample of blood Thus it appeared possible to increase the concentrations of serum sodium by restriction of fluid, but depression of the concentration below normal was not achieved by ingestion of large amounts of fluid In none of the samples of blood did the concentrations of potassium, calcium, phosphate or nonprotein nitrogen vary significantly from the average range for normal persons There was some increase in the value for

11 Veil, W H Ueber die Wirkung gesteigerter Wasserzufuhr auf Blutzusammensetzung und Wasserbilanz Beitrag zur Kenntnis der Polydipsie und des Diabetes insipidus, *Deutsches Arch f klin Med* **119** 376, 1916

12 Meyer, E, and Meyer-Bisch, R Beitrag zur Lehre von Diabetes insipidus *Deutsches Arch f klin Med* **137** 225, 1921

13 Butler, A M, Harper, E A, and Carey, B W, Jr Excretion of Sodium and Chloride in Normal Persons and in Patients with Nephritis and Diabetes Insipidus, *Am J Dis Child* **46** 1459 (Dec) 1933

TABLE 2—*Experimental Observations on Blood*

Date	Time, A M	Whole Blood		pH	Serum						Cells				Comment		
		Oxygen Capacity, mM per Liter	Cell Volume, Per Cent		Total Fixed Base, mEq per Liter	Sodium, mEq per Liter	Potas sium, mEq per Liter	Cal cium, mFq per Liter	Total CO ₂ , mM per Liter	Chlo ride, mEq per Liter	Phos phate, mEq per Liter	Pro tein, Gm per 100 Cc	Non protein Nitro gen, Mg per 100 Cc	Chlo ride, mEq per Liter		Water, Gm per Liter	Chloride Ratio
11/23/37	8	886	44.3	157.1	141.9	4.3	4.9	31.0	104.7	2.2	6.8	28				Mild thirst	
11/24/37	8	984	46.7	164.3	151.5	4.3	4.9	33.5	109.5	2.7	6.5	29				Intense thirst	
11/26/37	8	934	45.1	157.1	144.7	4.1	4.8	30.4	106.3	2.3	6.9	25				Mild thirst	
12/11/37	8		45.1	155.7	143.3	3.9	4.8	27.3	104.7	2.3	6.6	21				Mild thirst	
12/17/37	8	913	44.2	159.2	146.2	3.8	4.8	27.0	108.2	2.1	6.6	29				Moderate thirst	
12/18/37	8	940	44.9	162.1	148.7	3.9	5.0	26.0	111.2	2.3	6.9	25				Moderate thirst	
12/22/37	8	911	41.2	167.7	153.9	3.4	4.9	32.0	115.1	2.5	6.4	22				Intense thirst	
3/21/38	11		40.6	161.8	149.0						6.1					Moderate thirst	
3/24/38	8		43.3	164.7	152.0	1.0			111.4		6.9	13				Intense thirst	
3/24/38	11		42.5	164.7							6.7					Intense thirst	
3/31/38	8		38.4	163.2	150.5	3.6			112.1		6.0					Intense thirst	
3/31/38	11		37.3	164.1							5.7	18				Intense thirst	
4/ 6/38	8		38.9	152.3	142.5	3.6			101.6		6.1	23				Mild thirst	
4/ 6/38	11		36.6	157.1		3.6					6.1	22				Mild thirst	
10/22/38	8		46.3	156.8	142.5	4.0	4.9	26.5	101.5		7.1	34				Mild thirst	
10/29/38	8		41.1	153.4	142.0	1.0	4.9	28.0	100.7		6.9	33				Mild thirst	
11/ 7/38	8		42.8	156.5	145.1	4.5	5.0	26.9	106.7		6.9	29	15.2	713		Moderate thirst	
11/ 9/38	8		38.0	161.4	150.5	4.3	4.9	27.5	113.7		6.1	28	51.7	713		Intense thirst	
11/22/38	8		36.8	158.4	144.5	4.9		17.5	117.4		5.9		61.9	724		Mild thirst	
11/29/38	8		33.6	161.2	149.9	3.4		36.0	101.2		5.8	32	16.1	712		Mild thirst	

TABLE 3—*Body Weight, Fluid Intake and Data on Urine*

Period	Date	Body Weight, Kg	Fluid Intake, Cc	Volume, Cc	pH	Urine					Titratable Acid		Phosphate at pH of 7.1, mEq	Total Nitrogen, Gm	
						Specific Gravity	Ammonia N, mEq	Sodium, mEq	Potas sum, mEq	Calcium, mEq	Mag- nesum, mEq	Acid of 7.1, mEq			Chloride, mEq
I	12/11 15/37	76.5	4,000	4,690	6.7	1.003	44.5	35.4	38.4	9.1	0.1	22.0	41.4	25.1	9.6
	12/13 16/37	76.7	4,000	4,600	6.0	1.003	37.5	33.3	29.0	11.8	1.7	19.5	39.3	21.7	8.7
	12/16 17/37	76.6	1,000	4,830	6.1	1.033	35.0	34.5	31.7	10.5	1.5	23.0	41.1	22.1	8.9
II	12/17 18/37	76.7	180	2,630	5.8	*	35.0	39.4	37.3	10.1	5.9	21.0	19.3	21.8	8.7
	12/18 19/37	76.1	1,000	3,940	6.0	1.003	36.0	53.3	31.3	8.7	4.8	20.5	56.1	18.1	8.6
	12/19 20/37	76.6	1,000	4,180	6.0	1.004	34.5	52.5	36.5	12.6	5.5	20.5	60.2	20.1	8.7
III	12/20 21/37	76.1	4,000	3,630	6.4	1.006	32.5	174.8	65.6	9.9	5.3	18.5	195.0	26.3	8.8
	12/21 22/37	76.2	1,000	3,870	6.3	1.007	40.5	330.5	65.6	11.3	5.9	15.5	361.0	23.0	8.6
	12/22 23/37	75.9	4,000	3,930	6.3	1.005	35.5	186.0	40.2	9.6	4.1	15.0	191.5	19.3	9.0
IV	12/23 21/37	75.5	4,000	4,420	6.7	1.005	35.0	129.0	36.7	11.9	4.8	12.0	123.3	21.7	9.3
	10/25 26/38	69.1	1,000	3,680	5.9		41.1	10.2	11.2	9.9	6.1	27.2	18.8		12.1
	10/26 27/38	69.1	4,000	3,540	5.9		40.7	9.2	16.7	9.7	6.2	26.1	16.1		12.1
V	10/27 25/38	69.2	4,000	3,770	5.9		39.5	9.3	45.5	9.8	6.0	25.6	15.1		12.1
	10/28 29/38	69.0	1,000	3,650	5.9		37.7	8.5	45.5	8.9	1.8	23.8	12.3		12.1
	11/ 7 8/38	69.1	4,000	3,200	6.3		32.8	111.1	51.8	9.7	6.0	22.8	116.1		10.5
	11/ 8 9/38	69.9	4,000	3,410	6.4		37.2	240.1	59.6	11.1	6.0	20.1	256.0		9.3
	11/ 9 10/38	70.6	1,000	4,560	6.7		35.6	163.2	43.9	12.7	7.1	15.5	160.5		10.3
	11/10 11/38	69.8	4,000	4,190	6.8		28.9	101.8	42.9	10.1	4.6	15.1	88.8		9.9

* Specimens were partitioned and a maximum specific gravity of 1.011 was observed between 1.30 and 5.40 a m

total carbon dioxide during the first stay in the hospital. This was not observed subsequently except after ingestion of sodium bicarbonate.

Three weeks later these experiments were repeated, and collections of excreta were made. The first period (table 3) extended from December 14 to December 17. The fluid intake was maintained at 4,000 cc daily. The second period began December 17. The fluid intake on the first day was 180 cc, on the second and third day it was 4,000 cc. The third period lasted from December 20 to 24. The experimental conditions were similar to those of the first period, except that 20 Gm of sodium chloride was ingested daily on the first two days. The blood pressure in millimeters of mercury before ingestion of salt was 124 systolic and 88 diastolic. After the two days of salt ingestion it was 168 systolic and 108 diastolic. In each period an aliquot sample of one day's diet was dried and prepared for analysis of various constituents.

Samples of blood were taken on December 14, 17, 18 and 22. On December 17 there was an increase in concentration of total fixed base, sodium and chloride over the values observed on December 14. This is interpreted as evidence that the fluid requirements at this time were in excess of the 4,000 cc allowed daily. After twenty-four hours of rigid restriction of fluids the concentrations of sodium and chloride were similar to those observed in the previous dehydration experiment. The highest concentrations of serum sodium and chloride were observed after the ingestion of sodium chloride. The concentration of sodium was 153.9 milliequivalents and that of chloride 115.1 milliequivalents per liter. There was an increase of about 5 millimols per liter in concentration of serum carbon dioxide as compared with a maximum increase of 2.5 millimols in the dehydration experiments. As in the first experiments, minimal changes were observed in the concentrations of potassium, calcium, phosphate, protein and nonprotein nitrogen.

The data on intake and output are summarized in table 4. The "balance observations" for potassium, magnesium, phosphate and total nitrogen show that equilibrium was achieved for these substances. The body was not in equilibrium, however, in the exchange of calcium, sodium and chloride. A negative calcium balance was observed but not explained. Although the patient was confined to the metabolism ward, she was ambulatory, and it is doubtful if this imbalance can be attributed to inactivity. Roentgenograms of the skeleton showed no generalized decalcification, and it is presumed that the dissipation of calcium either was transient or had persisted for only a short time. An appreciable retention of sodium and chloride was observed in each period. The amount retained was dependent on intake and was greater during the period when extradietary salt was given.

The patient was admitted the second time for study of body fluid volumes (table 5) as well as for further study of serum electrolytes. On March 21, 750 cc of fluid was given between 7 and 7:30 a. m. At 8 a. m. Evans' blue dye (T-1824, Eastman Kodak Co.) and sodium thiocyanate were injected for determination of plasma volume and interstitial fluid volume. No further water was allowed until the experiment was finished. No symptoms of thirst were noticed during the determination of plasma volume. Moderate thirst developed before completion of the interstitial fluid volume experiment, at 11:30 a. m. These observations were used as controls for subsequent experiments.

The studies were repeated on March 24. One hundred and twenty cubic centimeters of extradietary water and the control diet were the only ingesta allowed in the thirty hours previous to the experiment. The volume of urine passed in the twenty-four hour period before the beginning of the experiment was 1,260 cc.

TABLE 4—*Summary of Certain Balance Data*

First Period, Dec 14 to 17, 1937							
	Sodium, mEq	Potassium, mEq	Calcium, mEq	Mag- nesium, mEq	Chloride, mEq	Phosphate, mEq	Total Nitrogen, Gm
Dietary intake	227	164	47	47	227	77	33
Urinary output	102	99	31	7	122	69	27
Fecal output	33	66	94	31	13	31	5
Daily balance	+30 6	— 0 4	—26 0	+ 3 4	+30 6	— 8 0	+ 0 4
Second Period, Dec 17 to 20, 1937							
	Sodium, mEq	Potassium, mEq	Calcium, mEq	Mag- nesium, mEq	Chloride, mEq	Phosphate, mEq	Total Nitrogen, Gm
Dietary intake	227	151	47	44	216	73	34
Urinary output	145	105	31	18	166	60	26
Fecal output	21	33	45	20	7	20	3
Daily balance	+19 0	+ 4 3	— 9 8	+ 2 1	+14 4	— 2 3	+ 1 5
Third Period, Dec 20 to 24, 1937							
	Sodium, mEq	Potassium, mEq	Calcium, mEq	Mag- nesium, mEq	Chloride, mEq	Phosphate, mEq	Total Nitrogen, Gm
Dietary intake	328	232	189	55	276	92	43
Extradietary intake	684				684		
Urinary output	830	208	43	20	871	92	36
Fecal output	35	46	178	26	15	29	6
Daily balance	+38 8	— 5 6	— 7 8	+ 2 2	+18 6	— 7 5	+ 0 4
Fourth Period, Oct 25 to 29, 1938							
	Sodium, mEq	Potassium, mEq	Calcium, mEq	Mag- nesium, mEq	Chloride, mEq	Phosphate, mEq	Total Nitrogen, Gm
Dietary intake	120	287	55		95	118	54
Extradietary intake							
Urinary output	37	179	38		62	101	49
Fecal output	30 0	83 0	30 6		16 5	28	5 7
Daily balance	+13 2	+ 6 2	— 3 5		+ 4 0	— 2 7	— 0 2
Fifth Period, Nov 7 to 11, 1938							
	Sodium, mEq	Potassium, mEq	Calcium, mEq	Mag- nesium, mEq	Chloride, mEq	Phosphate, mEq	Total Nitrogen, Gm
Dietary intake	136	279	48		100	119	50
Extradietary intake	684				684		
Urinary output	517	198	44		621	92	40
Fecal output	38 3	47 6	39 4		12 1	29	3 8
Daily balance	+66 2	+ 8 3	— 8 7		+37 6	— 0 5	+ 1 5

TABLE 5—*Experimental Observations on Volume of Body Fluids*

Date, 1938	Plasma Volume, Cc	Interstitial Fluid	
		Liters	Per Cent of Body Weight
March 21	2,580	15 5	20 8
March 24	2,450	15 0	20 4
March 31	2,740	15 7	21 5
April 6	2 800	16 7	23 4
October 29	2 580	15 2	22 1
November 22	3,440	15 4	22 5
November 29	3,440		

The body weight decreased 14 Kg. Symptoms of thirst were noted shortly after the beginning of abstinence from fluid and became intense before the end of the period. The buccal mucous membrane appeared to be very dry. The plasma and interstitial fluid volumes as determined during intense thirst showed only slight variation from those observed when thirst was less distressing. Plasma volume showed a maximum decrease of 130 cc, or 5 per cent, and interstitial fluid volume a decrease of 500 cc, or 3 per cent.

On each of the three consecutive days beginning March 28, 20 Gm of sodium chloride was given by mouth. The fluid intake was maintained at 4,000 cc. The volume studies were repeated March 31. Symptoms of thirst appeared to be as intense as during the dehydration experiment. The changes in body fluid volumes, however, were the reverse of those observed previously. The plasma volume increased 14 per cent, and the interstitial fluid volume increased 4 per cent. The value for serum base remained elevated, while that for serum protein decreased to 59 per cent, evidently the serum was diluted with slightly hypertonic physiologic solution of sodium chloride.

A control experiment was repeated on April 6. One thousand cubic centimeters of water was ingested thirty minutes before the test. During the test, thirst was slight. The plasma volume was 2,800 cc, the maximum observed in any experiment. The interstitial fluid volume was 167 Kg. This was 10 per cent greater than during the first experiment. The concentrations of total base, sodium and chloride in the serum were in the normal range.

Inulin and creatinine clearances (table 6) were determined on April 1. During three collection periods, the average inulin clearance was 93 cc per minute and the creatinine clearance was 139 cc per minute. These are considered as normal values. On April 11 these studies were repeated after injection of 0.5 cc of solution of posterior pituitary U. S. P. The creatinine clearance showed little change, while the inulin clearance increased 13 per cent, to 105 cc per minute.

The plasma and interstitial fluid volumes were determined on October 29 under conditions similar to those on March 21. The observations checked satisfactorily. On November 22 the volume studies were repeated. During the thirty-six hours before this test, 18 Gm of ammonium chloride was ingested. A daily intake of 4,000 cc of water was maintained. The patient denied having distressing symptoms of thirst during the test. The plasma volume increased 860 cc, or 33 per cent. No change was observed in the interstitial fluid volume. The values for serum sodium and total base were only slightly above normal. The value for serum chloride, however, was 117.5 milliequivalents per liter, and that for total carbon dioxide in the serum was 17.5 millimols per liter. This is indicative of severe chloride acidosis. One week later 40 Gm of sodium bicarbonate was given, and the tests were repeated. Minimal symptoms of thirst were present. The body weight increased 14 Kg with ingestion of alkali. The plasma volume remained unchanged. The determination of interstitial fluid volume was unsatisfactory owing to technical difficulties. The concentration of serum sodium was increased to 149.9 milliequivalents per liter. The value for serum chloride was 101.2 milliequivalents, and that for total carbon dioxide in the serum was 36 millimols, per liter.

The clearance tests for inulin, creatinine, sodium, chloride and potassium were repeated on three separate days. From October 29 to November 1 the total sodium chloride intake was restricted to 15 Gm daily. Observations on renal clearance were made on November 1. The clearances of inulin and creatinine were similar to those of April 1. The clearances of sodium and chloride, how-

TABLE 6—*Experimental Observations on Renal Clearance*

Date, 1938	Time, A M	Urine Flow, Cc per Minute	Inulin			Creatinine		Sodium, Cc		Chloride, Potassium, Cc		Specific Gravity of Urine	Blood Pressure	Comment
			Cc Cleared per Minute	Plasma Cleared per Minute	Urine Plasma Ratio	Plasma Cleared per Minute	Creatinine Inulin Ratio	Plasma Cleared per Minute	Plasma Cleared per Minute	Plasma Cleared per Minute	Plasma Cleared per Minute			
April 1	9 48 10 00	12.2	100		8.2	137	1.37					1.009		
	10 00 10 24	11.0	91		8.2	137	1.51					1.007		
	10 24 10 35	10.8	87		8.1	144	1.67					1.005		
April 12*	9 13 9 26	2.46	115		46.5	124	1.09					1.030	136/86†	0.5 cc solution of posterior pituitary U S P given hypodermically at 7 a m
	9 26 9 37	2.91	107		36.7	131	1.23					1.018	120/84	
	9 37 9 50	2.49	93		37.5	125	1.35					1.014	120/80	
November, 1	9 31 9 41	9.6	78		8.1	119	1.53	0.15	0.52		8.2			Preceded by a low salt diet for 3 days
	9 41 9 51	10.4	86		8.1	128	1.49	0.19	0.56		8.8			
	9 51 10 01	12.4	101		8.1	150	1.48	0.21	0.64		10.6			
November 11	9 34 9 44	9.4	76		8.1	137	1.80	2.10			8.0			Preceded by a high salt diet for 3 days
	9 44 9 54	11.0	88		8.0	132	1.50	3.40			9.2			
	9 54 10 04	10.3	105		10.2	159	1.51	3.50			12.5			
November 19§	9 12 9 22	2.6	122		46.8	192	1.57	1.20	1.99		8.6			0.5 cc solution of posterior pituitary U S P given hypodermically at 6.45 a m
	9 22 9 42	2.8	135		48.6	167	1.24	1.00	1.64		7.9			

* The urine flow following injection of solution of posterior pituitary was 18 cc from 7 to 8 a m and 74 cc from 8 to 9 13 a m

† The blood pressure at 7 a m was 124/70 and at 8 50 a m was 140/88

§ The urine flow following injection of solution of posterior pituitary was 48 cc from 7 to 8 a m and 82 cc from 8 to 9 12 a m

ever, which were determined for the first time in this case, were considerably less than the average range for normal persons. In a study of 10 patients with various disorders but with normal ability to clear plasma of inulin (95 cc or more per minute) the average rate of sodium clearance was 160 cc per minute and that of chloride clearance 247 cc per minute¹⁴. After restriction of sodium chloride the patient under discussion showed a sodium clearance of 0.18 cc of plasma per minute and a chloride clearance of 0.58 cc of plasma per minute. After a high sodium chloride intake (20 Gm of sodium chloride per day for two days and 8 Gm on the morning before beginning the test) the clearances were redetermined. Inulin and creatinine clearances were unchanged from the previous observations. Sodium clearance increased more than tenfold. Samples for chloride concentration were destroyed inadvertently. The last series of clearance tests was done on November 19. Shortly before the test, 0.5 cc of solution of posterior pituitary U. S. P. was given. Reduction in the flow of urine was apparent, with an elevated clearance of all of the constituents determined except potassium. The sodium clearance was equivalent to 110 cc of plasma cleared per minute, and the chloride clearance, to about 180 cc per minute. The values for potassium clearance were similar in the 3 experiments.

COMMENT

All of the criteria necessary for a diagnosis of diabetes mellitus were satisfied. The development of diabetes mellitus in a sister of the patient is significant. The symptoms—polyuria, polydipsia, pruritus vulvae and loss of weight—are characteristic. Glycosuria and a diabetic type of blood sugar response following ingestion of 100 Gm each of three sugars confirm the presumptive diagnosis. Symptomatic relief after insulin treatment and, later, after moderate restriction of carbohydrate consumption is additional evidence.

Equally adequate data were obtained to substantiate a diagnosis of diabetes insipidus. Intense thirst was persistent through the day and wakened the patient intermittently at night. When fluid was allowed ad libitum, the daily intake varied between 5 and 8 liters. When fluids were forced, satiation was not achieved until more than 10 liters had been consumed. Other causes of persistent polydipsia and polyuria, such as Bright's disease and emotional polydipsia, were considered to be unlikely. Also, agents or syndromes which produce symptomatic diabetes insipidus,¹⁵ such as trauma to the hypothalamus, encephalitis, syphilis of the central nervous system and xanthomatosis, were believed to have been excluded.

14 Talbott, J. H., Coombs, F. S., Consolazio, W. V., and Pecora, L. J. Unpublished data.

15 (a) Weir, J. F., Larson, E. E., and Rowntree, L. G. Studies in Diabetes Insipidus, Water Balance and Water Intoxication. Study I, *Arch Int Med* 29:306 (March) 1922. (b) Warkany, J., and Mitchell, A. G. Diabetes Insipidus in Children. A Critical Review of Etiology, Diagnosis and Treatment, with Report of Four Cases, *Am J Dis Child* 57:603 (March) 1939.

The urine passed was of low specific gravity, usually 1 003 to 1 006. The maximum value observed during dehydration was 1 011. After injection of solution of posterior pituitary the maximum was 1 030. The abnormally high concentrations of sodium and chloride in the serum are interpreted as further evidence in support of a diagnosis of diabetes insipidus. The value for serum sodium usually was high normal or above normal. Maximum concentrations were observed after abstinence from fluid for thirty hours and after ingestion of large amounts of sodium chloride. During an elapsed time of more than a year, the value for serum sodium varied between 142 and 150 milliequivalents per liter at twelve determinations. It was greater than 150 milliequivalents per liter at five determinations. The changes in the concentration of sodium were accompanied by a molar equivalent increase in that of total fixed base. The concentration of serum chloride was increased less constantly than that of sodium. In only six of the samples was it greater than 110 milliequivalents per liter. These changes are the basis for the statement made previously that this type of diabetes insipidus should be termed "hypernatremic" rather than "hyperchloremic."

Butler and his associates¹³ have reported concentrations of the same magnitude in 1 patient with diabetes insipidus. Peters,^{3a} in a summary of the literature, concluded that there are no characteristic changes in the concentration of constituents of the blood, although he referred to 1 patient¹⁶ in whose case a serum sodium concentration of 147.2 milliequivalents per liter was recorded. We prefer to attach considerable significance to an elevation of this magnitude. In normal persons some increase in the values for serum sodium and total base may accompany ingestion of large amounts of sodium chloride.¹⁷ Concentrations similar to those observed in this patient, however, are seen only in dyscrasias associated with a profound disturbance of the acid-base balance of the body.

It is important to emphasize that the increased concentration of serum sodium was achieved with minimal variations in serum protein, calcium and potassium and in cell volume. The syndrome does not have, therefore, the characteristics of dehydration with which one is accustomed to associate excessive loss of fluid from the body.

The pathogenesis in human beings of diabetes mellitus as well as of diabetes insipidus remains to be defined. In experimental animals, von Mering and Minkowski showed that surgical removal of the pancreas produced a disease which resembled diabetes mellitus. The

16 Laviates, P. H., D'Esopo, L. M., and Harrison, H. E. The Water and Base Balance of the Body, *J. Clin. Investigation* **14** 251, 1935.

17 Loeb, R. F., Atchley, D. W., Richards, D. W., Jr., Benedict, E. M., and Driscoll, M. E. On the Mechanism of Nephrotic Edema, *J. Clin. Investigation* **11** 621, 1932.

anatomic changes in the pancreas which have been observed at necropsy in patients with clinical diabetes, however, are disappointing. Recently, Houssay¹⁸ and Long¹⁹ have noted that the development of so-called pancreatic diabetes may be prevented by hypophysectomy. These experiments gave rise to the hypothesis that sugar diabetes is related to a hypersecretion of the diabetogenic hormone from the anterior lobe of the pituitary. Young²⁰ was the first who was successful in producing hyperglycemia in animals by injection of pituitary extracts. While these observations are pertinent to our argument, it is not believed to be proved that the common variety of clinical diabetes mellitus is dependent on hyperfunctioning cells of the anterior lobe of the hypophysis.

The pathogenesis of human diabetes insipidus is equally uncertain. Fisher, Ingram and Ransom^{3b} have produced permanent polyuria in animals by interruption of the nervous pathway from the nucleus supra-opticus to the hypophysis, with atrophy of the pars nervosa. These changes were thought to be accompanied by a decreased elaboration of the antidiuretic, pressor and oxytocic substances. In human beings as well as in animals, surgical removal of the whole pituitary gland or destruction by massive tumors with interruption of the supraoptico-hypophysial tract does not result in permanent diabetes insipidus. There is, therefore, anatomic evidence which suggests that clinical diabetes insipidus is dependent on a functioning anterior lobe²¹ as well as interruption of certain pathways to the posterior lobe. Beyond this there is little concurring evidence.

In the patient under consideration we should like to believe that the two types of diabetes have a related pathogenesis²². Increased elaboration of the diabetogenic hormone from hyperplasia of the cells of the anterior lobe of the pituitary with secondary effects from pressure on the supraopticohypophysial tract constitutes a satisfactory working hypothesis.

18 Houssay, B. A. Carbohydrate Metabolism, New England J. Med. **214** 971, 1936.

19 Long, C. N. H. The Influence of the Pituitary and Adrenal Glands upon Pancreatic Diabetes, Medicine **16** 215, 1937.

20 Young, F. G. Experimental Investigations on Relationship of Anterior Hypophysis to Diabetes Mellitus, Proc. Roy. Soc. Med. **31** 1305, 1938.

21 von Hann, F. V. Ueber die Bedeutung der Hypophysenveränderungen bei Diabetes insipidus, Frankfurt Ztschr. f. Path. **21** 337, 1918. Richter, C. P. Experimental Diabetes Insipidus. Its Relationship to the Anterior and Posterior Lobes of the Hypophysis, Am. J. Physiol. **110** 439, 1934.

22 Gellerstedt, N., and Grill, C. A Clinical and Anatomic Contribution to the Knowledge of Combined Diabetes Mellitus and Insipidus. Report of a Case Treated with Insulin and Salyrgan in Which the Patient Died with Symptoms of Hypoglycemia, Acta med. Scandinav. **75** 586, 1931. Steel, R. S. Diabetes and Dyspituitarism, Proc. Staff Meet., Mayo Clin. **2** 216, 1927. Greene and Gibson^{2a}

The incidence of glycosuria, hyperglycemia and even frank diabetes mellitus in patients with pituitary tumors of various types speaks for the explanation²³ The chronologic order of development of symptoms supports the hypothesis Convincing arguments against this explanation are the infrequent occurrence of polyuria in patients with a pituitary tumor and the resistance to insulin²⁴ frequently observed in such syndromes

The participation of other endocrine glands in the syndrome was not apparent The basal metabolic rate was within the normal range at two examinations Menstruation had not been observed for fourteen years, but the presence of hot flashes during the menopause indicated primary gonadal hypofunction and not hypofunction secondary to a pituitary lesion

The data on balance (tables 2, 3 and 4) show a retention of sodium and chloride in each of the five periods Similar findings have been reported by Peters²⁵ and Weir²⁶ in studies on patients with diabetes insipidus receiving a high sodium chloride intake In our patient the positive balance was accompanied by an increased concentration of these constituents in the serum The body weight and body fluid volumes showed little change during the respective periods of observation The retention of sodium and chloride, then, must have been achieved by an increase in concentration in body fluids without a concomitant retention of water The observations fail to substantiate the hypothesis of Stehle²⁶ that the polyuria of diabetes insipidus is a salt diuresis from inability of the tissues to retain salt In this syndrome the tissues retain salt with ease, to relinquish it is difficult

Retention of sodium chloride without retention of water is encountered infrequently in experimental medicine The mechanism may be attributed either to a quantitative diminution in rate of filtration of plasma through the renal glomeruli or to increased reabsorption of sodium chloride by the tubules The values for inulin clearance in this case showed a normal filtration rate This agrees with the observations made on creatinine clearance by Butler and his associates¹³ If a normal filtration rate is accepted, then increased tubular reabsorption must be considered in any attempt to explain the phenomenon Threshold sub-

23 Cushing, H The Basophil Adenomas of the Pituitary Body and Their Clinical Manifestations (Pituitary Basophilism), *Bull Johns Hopkins Hosp* **50**: 137, 1932

24 Davidoff, L M, and Cushing, H Studies in Acromegaly VI The Disturbance of Carbohydrate Metabolism, *Arch Int Med* **39** 751 (June) 1927

25 Weir, J F Observations on the Influence of Pituitary Extract on the Metabolism in Diabetes Insipidus, *Arch Int Med* **32** 617 (Oct) 1923

26 Stehle, R L The Diuretic-Antidiuretic Action of Pituitary Extract, *Am J Physiol* **79** 289, 1927

stances, such as sodium and chloride, should show a diminished clearance if tubular reabsorption is increased above normal. The data confirm this presumption. Sodium and chloride clearances on Nov 1, 1938 were well below normal. On November 19, injection of solution of posterior pituitary caused an increase in clearance rates, but normal values were not achieved. A high sodium chloride intake (November 11) proved the only effective means of increasing the clearance rates of the respective substances above normal. Increased reabsorption of sodium chloride, therefore, is believed to be an important pathogenic mechanism in the production of diabetes insipidus. This action is essentially the opposite of that in adrenal insufficiency, a condition associated with decreased tubular reabsorption of sodium and chloride.²⁷

Inspection of the data reveals that the retention of electrolytes and disturbance of renal clearance were confined to sodium and chloride. The values for potassium, calcium and phosphate clearance were normal. It is important for our argument to stress the point that approximate nitrogen equilibrium was achieved during each experimental period. The changing state applied only to sodium and chloride.

The filtration rate as measured by inulin clearance was increased slightly after injection of solution of posterior pituitary. This does not agree precisely with the study of Burgess, Harvey and Marshall²⁸ who observed no increase in xylose clearance in dogs under similar conditions. Since some xylose is reabsorbed by the renal tubules, the experiments are not strictly comparable. Our observations suggest that posterior pituitary has a diuretic²⁹ action, i e., an increase in glomerular filtration. This is ineffective, however, because the principal action is antidiuretic, i e., reabsorption of water by the tubules.

In concluding the discussion of renal function in patients with diabetes insipidus, attention should be called to the changing clearances in consecutive ten minute periods. Many clearance determinations have been made by us during the past three years for patients with normal and pathologic kidneys. With the technic employed, inulin and creatinine values for other patients have been remarkably constant during consecutive collection periods.³⁰ It is believed that the results in this

27 Gersh, I, and Grollman, A. Kidney Function in Adrenal Cortical Insufficiency, *Am J Physiol* **125** 66, 1939.

28 Burgess, W W, Harvey, A M, and Marshall, E K, Jr. The Site of the Antidiuretic Action of Pituitary Extract, *J Pharmacol & Exper Therap* **49** 237, 1933.

29 Bourquin, H. Studies on Diabetes Insipidus. II The Diuretic Substance, Preliminary Observations, *Am J Physiol* **83** 125, 1927.

30 Smith, H W. The Physiology of the Kidney, New York, Oxford University Press, 1937.

patient should not be attributed to technical errors. Continuously changing renal function seems to us to be a more acceptable explanation.

An interesting by-product of this investigation were the conclusions concerning the mechanism of thirst. Thirst apparently is insatiable in cases of untreated diabetes insipidus and as a symptom has received considerable attention in this syndrome. Conclusions derived from this and similar studies may not be utilized directly to augment understanding of thirst in normal persons. Certain implications, however, are noteworthy and may be significant. Changes in plasma volume, interstitial fluid volume and concentrations of sodium chloride in the blood, individually or in association, have been thought to be important in the pathogenesis of thirst. Weir and his associates^{15a} observed normal blood and plasma volumes in patients with diabetes insipidus. No change in volumes after injection of solution of posterior pituitary was observed. Our data, which comprise, in addition, records of interstitial fluid volume are in agreement. Only small changes in body fluid volumes followed abstinence from fluid or ingestion of sodium chloride, although thirst, which accompanied many of the experimental procedures, was intense.

It may be argued that the increased concentrations of serum sodium and chloride were responsible for the intense symptoms. An increased concentration of either sodium or chloride without concomitant elevation of the other will not produce intense thirst. Thus, on Nov 22, 1938, the concentration of serum chloride was 117.4 milliequivalents, and that of serum sodium, 144.5 milliequivalents, per liter. The volume of plasma was increased, and thirst was minimal. One week later the concentration of serum sodium was 149.9 milliequivalents and that of serum chloride 101.2 milliequivalents per liter, and the plasma volume was 3,440 cc. Again, thirst was minimal. The hypothesis of Arden³¹ that thirst is governed by sodium alone was not confirmed by these experiments.

The conclusion seems inescapable that, just as respiration is controlled by several factors,³² so thirst is controlled by several factors.³³ Dryness of the mouth as a local process³⁴ or as a result of general depletion of body water³⁵ may account for thirst at times. An increased

31 Arden, F. Experimental Observations upon Thirst and on Potassium Overdosage, *Australian J. Exper. Biol. & Med. Sci.* **12** 121, 1934.

32 Henderson, L. J. *Blood: A Study in General Physiology*, New Haven, Conn., Yale University Press, 1928.

33 Dill, D. B. *Life, Heat and Altitude: Physiological Effects of Hot Climates and Great Heights*, Cambridge, Mass., Harvard University Press, 1938.

34 Cannon, W. B. The Physiological Basis of Thirst. Croonian Lecture, *Proc. Roy. Soc., London, Ser. B* **90** 283, 1918.

35 Gregersen, M. I., and Cannon, W. B. Studies on the Regulation of Water Intake. I. The Effect of Extirpation of the Salivary Glands on the Water Intake of Dogs While Panting, *Am. J. Physiol.* **102** 336, 1932.

concentration of serum sodium and chloride without depletion of plasma or interstitial fluid volume and without reduction of water in the blood cells appears to be important at other times

SUMMARY AND CONCLUSIONS

Metabolic studies on a patient with diabetes mellitus and diabetes insipidus are described. The clinical diagnosis of both dyscrasias appeared to be confirmed by the laboratory data. In an attempt to explain both endocrine dysfunctions by a single lesion, it was suggested that a hyperplastic and hyperfunctioning anterior pituitary lobe might have encroached on the supraopticohypophysial pathway. A presumption of pituitary tumor was substantiated by roentgen examination. Chronologically, symptoms of diabetes mellitus preceded those of diabetes insipidus. Increased elaboration of the diabetogenic hormone from the cells of the anterior lobe was believed to be responsible for the symptoms of diabetes mellitus. Interruption of at least one nerve tract to the posterior lobe was believed to be responsible for the symptoms of diabetes insipidus.

The concentrations of serum sodium and chloride were increased at many observations. The diagnostic significance of these abnormalities is stressed.

All of the precise tests of renal function except those for sodium and chloride clearance resulted in values within the normal range. The decreased clearance of sodium and chloride and the unimpaired clearance of inulin and creatinine suggest that the inherent defect in diabetes insipidus is increased reabsorption of sodium chloride by the renal tubules. Injection of solution of posterior pituitary corrected this dysfunction temporarily. Further evidence of increased reabsorption was the positive balance for sodium and chloride during the five periods of controlled intake and output.

Symptoms of thirst were severe when the concentrations of serum sodium and chloride were increased simultaneously. Large changes in volume of plasma or interstitial fluid did not accompany aggravation or alleviation of this distressing symptom.

The patient described in this study was referred to us by Dr. James H. Townsend. Dr. Homer Smith helped with the preparation of the manuscript.

ARTERIAL BLOOD PRESSURE IN CASES OF AURICULAR FIBRILLATION, MEASURED DIRECTLY

W C BUCHBINDER, M D

AND

H SUGARMAN, M D

CHICAGO

It is well recognized clinically that in patients having auricular fibrillation or flutter with grossly irregular pulses determinations of the blood pressure by the ordinary auscultatory and palpatory methods not only are difficult to obtain but are subject to considerable error. Several methods have been suggested by which the average systolic blood pressure may be obtained,¹ and these, in general, are based on the number of pulse beats which come through or fail to come through at different cuff pressures. These indirect methods require two observers and laborious calculations, and their significance may be questioned on theoretic grounds. Because of this unsatisfactory situation we felt it desirable to reinvestigate this subject by actually determining the blood pressure directly by intra-arterial puncture. This we felt would permit us not only to obtain the actual values but to establish the factors responsible for their variation from beat to beat.

The Hamilton needle manometer, recently developed,² was available for this purpose. It has been definitely shown to be an accurate instrument and has been used by Woodbury, Robinow and Hamilton³ in studies on man.

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From the Cardiovascular Department, Michael Reese Hospital

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1 Silberberg, M. D. A Note on Blood Pressure Readings in Cases of Auricular Fibrillation, *Brit. M. J.* **1** 775, 1912. James, W. B., and Hart, T. S. Auricular Fibrillation. Clinical Observations on Pulse Deficit, Digitalis and Blood Pressure, *Am. J. M. Sc.* **147** 63 (Jan.) 1914. Kilgore, E. S. The Fractional Method of Blood Pressure Determination. A Contribution to the Study of Blood Pressure in Cardiac Arrhythmias, *Arch. Int. Med.* **16** 939 (Dec.) 1915.

2 Hamilton, W. F., Brewer, G., and Brotman, I. Pressure Pulse Contours in the Intact Animal. Analytical Description of a New High-Frequency Hypodermic Manometer with Illustrative Curves of Simultaneous Arterial and Intra-Cardiac Pressures, *Am. J. Physiol.* **107**:427 (Feb.) 1934.

3 Woodbury, R. A., Robinow, M., and Hamilton, W. F. Blood Pressure Studies on Infants, *Am. J. Physiol.* **122** 472 (May) 1938.

METHOD

The modification of the Hamilton manometer devised by Jochim and Gaddas⁴ is shown in figure 1. The equipment is mounted rigidly on a heavy jack (*J*) with a three point contact (*X*), one part of which is adjustable with the floor. The Hamilton manometer is lined up with the electrocardiograph machine so that it will record on one half of the photosensitive paper in a manner similar to the arrangement devised for other purposes in this laboratory.⁵ An ordinary 6 volt automobile headlight bulb is mounted in a housing (*A*) with a narrow vertical

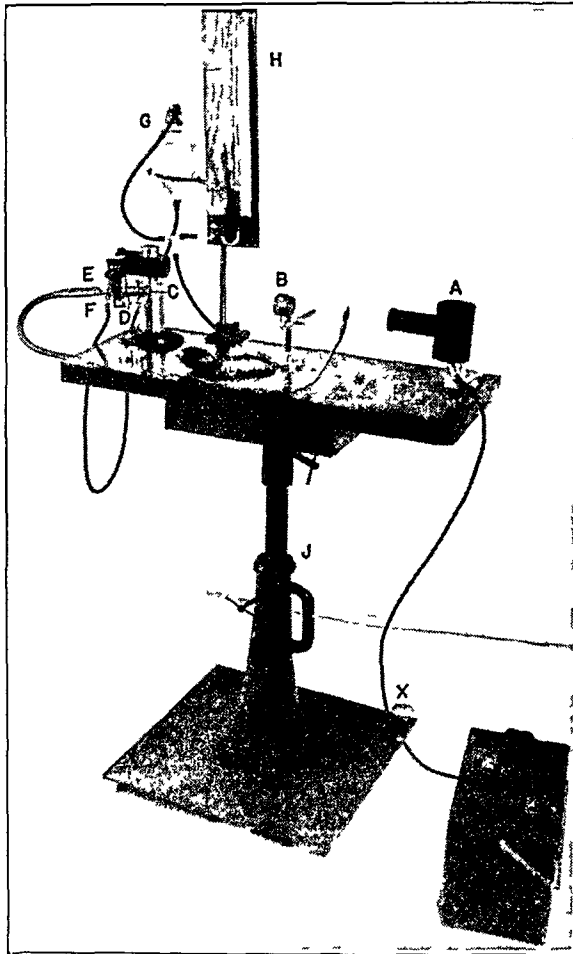


Fig 1—Photograph of the modification of the Hamilton manometer assembly, designed by Jochim and Gaddas and used in this study. See text for discussion.

slit in front. The image of the slit is converged by a double convex lens (*B*) and directed onto a planoconcave mirror (*C*) on the manometer, which reflects the image back onto the slit of the camera. By proper adjustment of the lens (*B*) the image of the slit can be sharply focused on the photosensitive paper. The manometer itself, which is an exact model of the one designed by Hamilton,

⁴ Jochim, K, and Gaddas, S. F. Unpublished data.

⁵ Jochim, K, Gaddas, S. F., and Marquis, H. A Mobile Unit for Simultaneously Recording Heart Sounds, Pulse Tracing and Electrocardiogram, *Am Heart J* **13** 731 (June) 1937.

is held rigidly in a metal tube (*D*) and supported by eight adjustable screws which can shift its direction. The metal tube is mounted rigidly on an upright bar by means of a tight-fitting clamp (*E*) so that the level of the manometer mirror (*C*) can be brought into the same plane as the optical axis of the electrocardiographic machine, thereby avoiding parallax. Cruder vertical adjustment is possible with the heavy jack. The whole unit is mobile. Silver membranes of

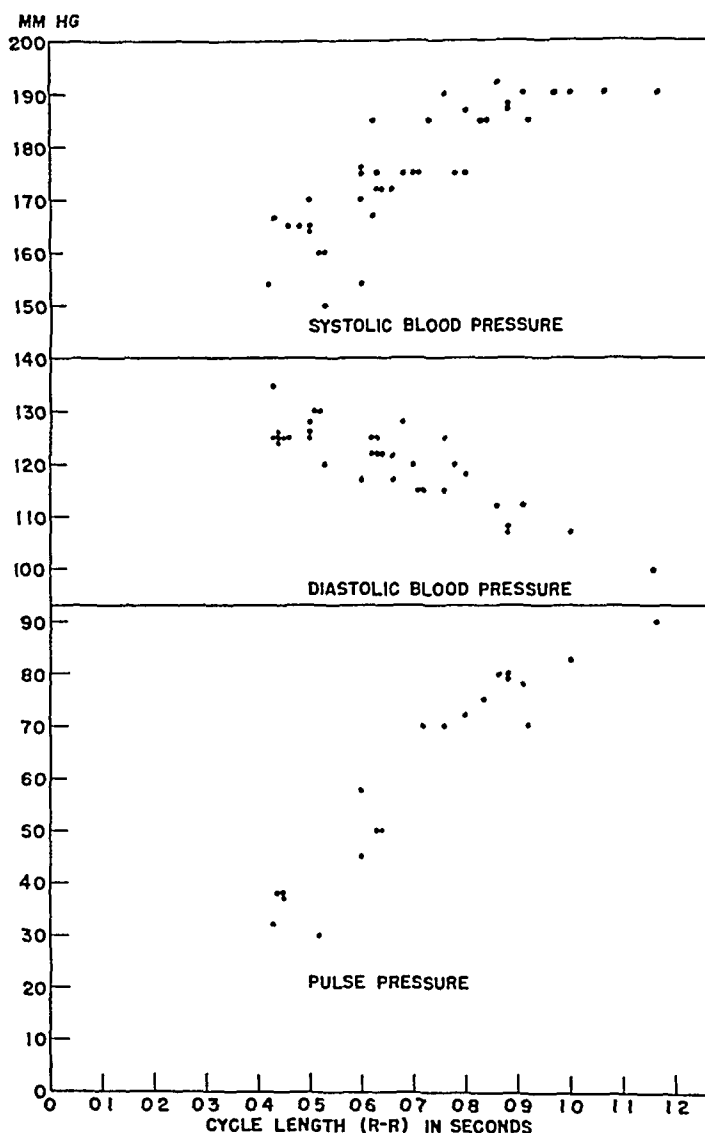


Fig 2—Chart showing the relation of systolic, diastolic and pulse pressure to cycle length in 50 successive beats of the heart of a patient with auricular fibrillation (a portion of whose record is shown in figure 6C). Ordinates, millimeters of mercury, abscissas, seconds. See text for discussion.

appropriate sensitivity, prepared by Mr S Rodbard, were employed to prevent distortion of the pressure curves. By means of a stopcock (*F*) the manometer is connected to a citrate leveling reservoir (*G*) and a mercury manometer (*H*) for calibration.

The system is sterilized by filling it for several days before use with a solution of 70 per cent alcohol. The alcohol is then replaced by a sterile solution of 4 per cent sodium citrate from which the air has been previously boiled off. This is

layered with sterile liquid petrolatum to keep the system free of air and to prevent it from becoming underdamped

The subject is permitted to lie comfortably in the recumbent or semiprone position, and the electrocardiographic leads are applied (leads II or III). A 20 gage needle soldered to an attachment which is screwed to the lead manometer tubing is inserted into the brachial artery after the skin has been previously sterilized with alcohol and anesthetized with a 1 per cent solution of procaine

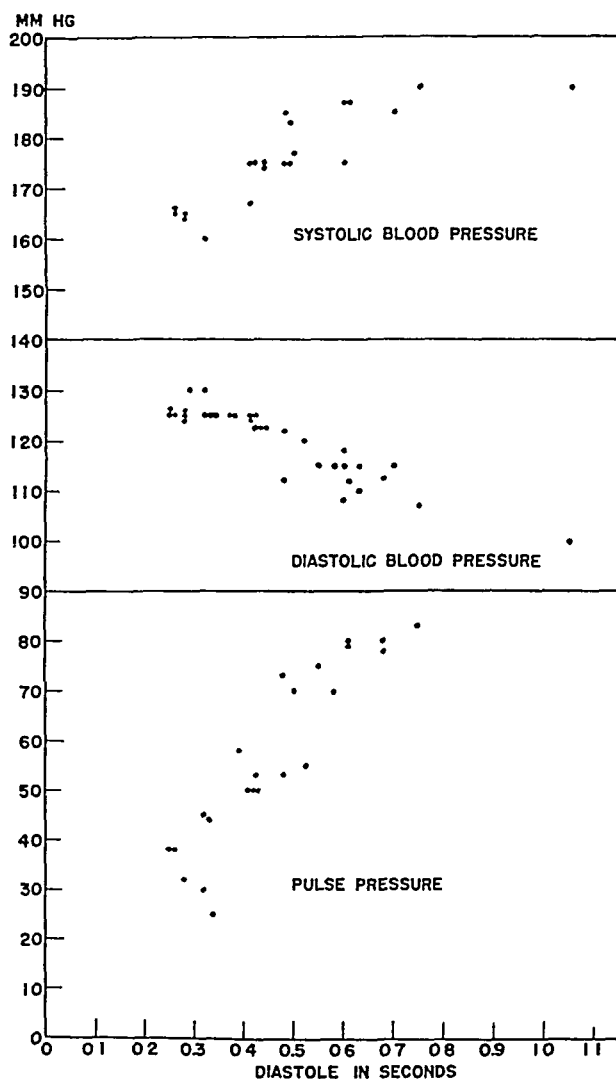


Fig 3—Chart constructed as in figure 2, relating the variables to the preceding diastole. See text for discussion.

hydrochloride. The appearance of pulsations of the image on the camera slit indicates that the needle is in the artery. After a record of the pressure has been taken simultaneously with the electrocardiogram, the pressure manometer is calibrated in the usual manner,⁶ and the calibration is photographed so that the pressure levels can be quantitated.

⁶ Katz, L. N., Friedman, M., Rodbard, S., and Weinstein, W. Observations on the Genesis of Renal Hypertension, *Am Heart J* **17** 334 (March) 1939.

The clinical material was obtained from the medical wards of the hospital and the adult cardiac clinic of the Mandel Clinic. Ten patients were used in this study. All were suffering from organic heart disease, in 6 it was of the rheumatic type, and in 4, of the arteriosclerotic type. Eight had chronic auricular fibrillation, 1 had chronic auricular flutter and 1 had sinus rhythm with a pulsus trigeminus due to regularly recurring auricular extrasystoles. (In addition, records were taken of several other patients with sinus rhythm [cf fig 14] and of others with frequent extrasystoles [cf fig 11].) Mitral stenosis was present in 3 of these patients and aortic insufficiency in 2. Two patients had marked hypertension. The ventricular rate in these patients at the time the records were obtained ranged

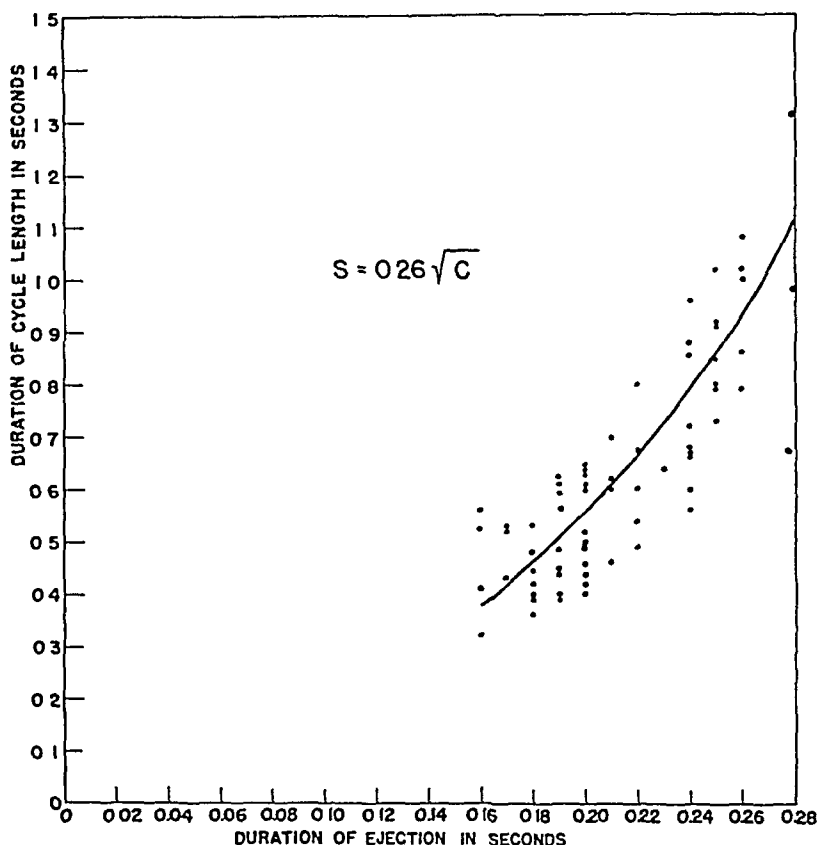


Fig 4—Chart relating the duration of ejection (abscissas) to the cycle length (ordinates) of 150 beats of the heart of a patient, portions of whose records are shown in figure 6 (*A*, *B* and *C*). The curve connects the means, and the equation for this curve is given in the chart. See text for discussion.

from an average rate of 161 beats per minute (cf fig 8*A*) to 36 beats per minute (cf fig 8*C*) in a case of auricular fibrillation with almost complete heart block due to digitalis excess. Two patients entered the hospital with severe congestive failure, and several records were taken on them during the course of clinical improvement (cf fig 6).

In each record the following measurements were made in 50 consecutive beats (cf fig 14*A*): (1) the cycle length from the RR interval of the electrocardiogram, lead II or III, (2) the maximum systolic pressure from the peak (*b*) of the pressure pulse curve, (3) the minimum diastolic pressure from the lowest point, *a*, on the pressure pulse curve, (4) the duration of ejection from the beginning of the upstroke of the pressure pulse curve to the bottom of the *incisura*

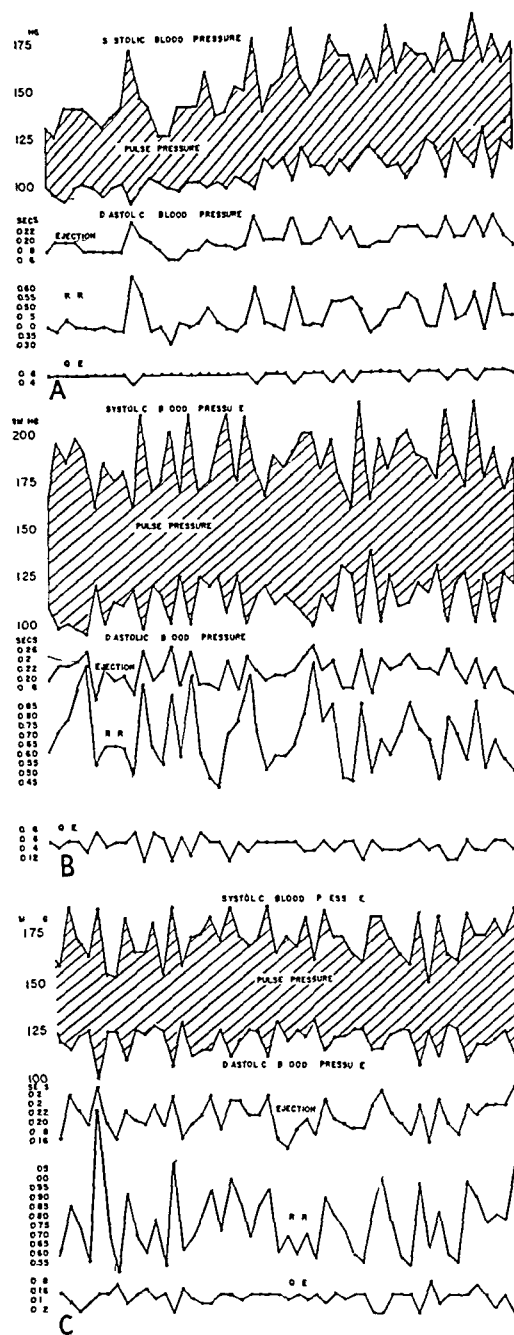


Fig 5—Charts showing the systolic blood pressure (uppermost curve), diastolic blood pressure (curve below), pulse pressure (shaded area), duration of ejection, RR interval and QE duration (successively lower curves) in 50 successive beats of the heart of a patient, portions of whose original record are shown in figure 6. Each beat is plotted in succession. The ordinates give millimeters of mercury for the pressures and seconds for the other measurements. The record in chart *A* was taken during heart failure, those in charts *B* and *C*, at two stages during recovery from heart failure. The method of determining these variables and their interpretation are discussed in the text.

(*a-c*), (5) the duration of diastole (and isometric contraction period) from the bottom of the incisura to the beginning of the upstroke of the pressure pulse (*c-a*) and (6) the QE interval, i.e., the interval between the beginning of QRS in the electrocardiogram to the upstroke of the pressure pulse curve (*Q-a*). The durations were determined in hundredths of a second and the pressures in millimeters of mercury.

The relation of the following factors to preceding cycle length and to the diastole preceding the measurement was analyzed: (*a*) systolic pressure, (*b*) diastolic pressure, (*c*) pulse pressure (computed by the difference between systolic and diastolic pressure), and (*d*) QE interval. These were assembled in tabular form, and graphs were then constructed to illustrate the relation. Other graphs

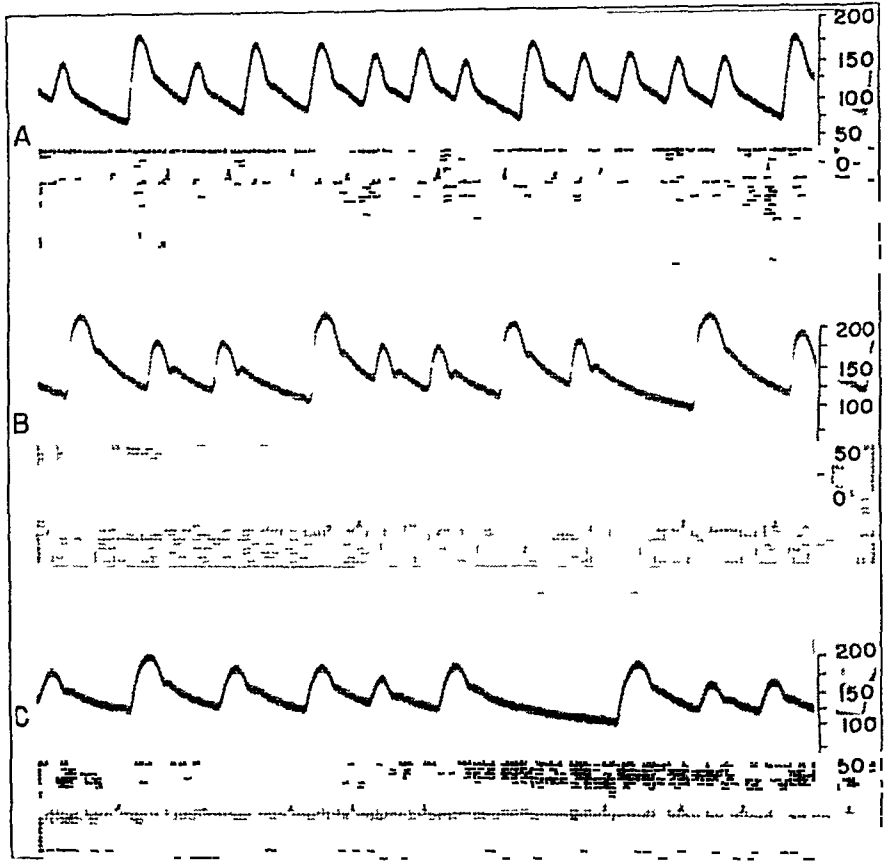


Fig 6—Portions of the original records (reduced) of a patient with auricular fibrillation at various stages of heart failure (*A*, maximum, *B*, intermediate, *C*, minimum). In each the direct pressure curve from the brachial artery is shown by the upper black curve, the calibration in millimeters of mercury is shown on the right. The standardized electrocardiogram, lead II, is shown by the white curve in each (time, 0.04 and 0.2 seconds). Each horizontal white line represents 0.1 millivolt.

were made to show the relation of the duration of ejection to the cycle length, when the variations in the latter were great enough a curve of the mean values was drawn, and the value for K which made the best fit to the curve was derived (by Mr. K. Jochim) by use of the formula $S = K \sqrt{C}$.

7. Katz, L. N., and Feil, H. S. Clinical Observations on the Dynamics of Ventricular Systole. Auricular Fibrillation, *Arch Int Med* 32: 672 (Nov) 1923.

RESULTS

An idea of the values for pressure is readily obtained by reference to our records (cf figs 6, 8 and 9). Superficial examination of the curves will show differences in both systolic and diastolic blood pressure with every beat during the irregular beating of the heart, the usual variation between successive beats being about 25 mm of systolic pres-

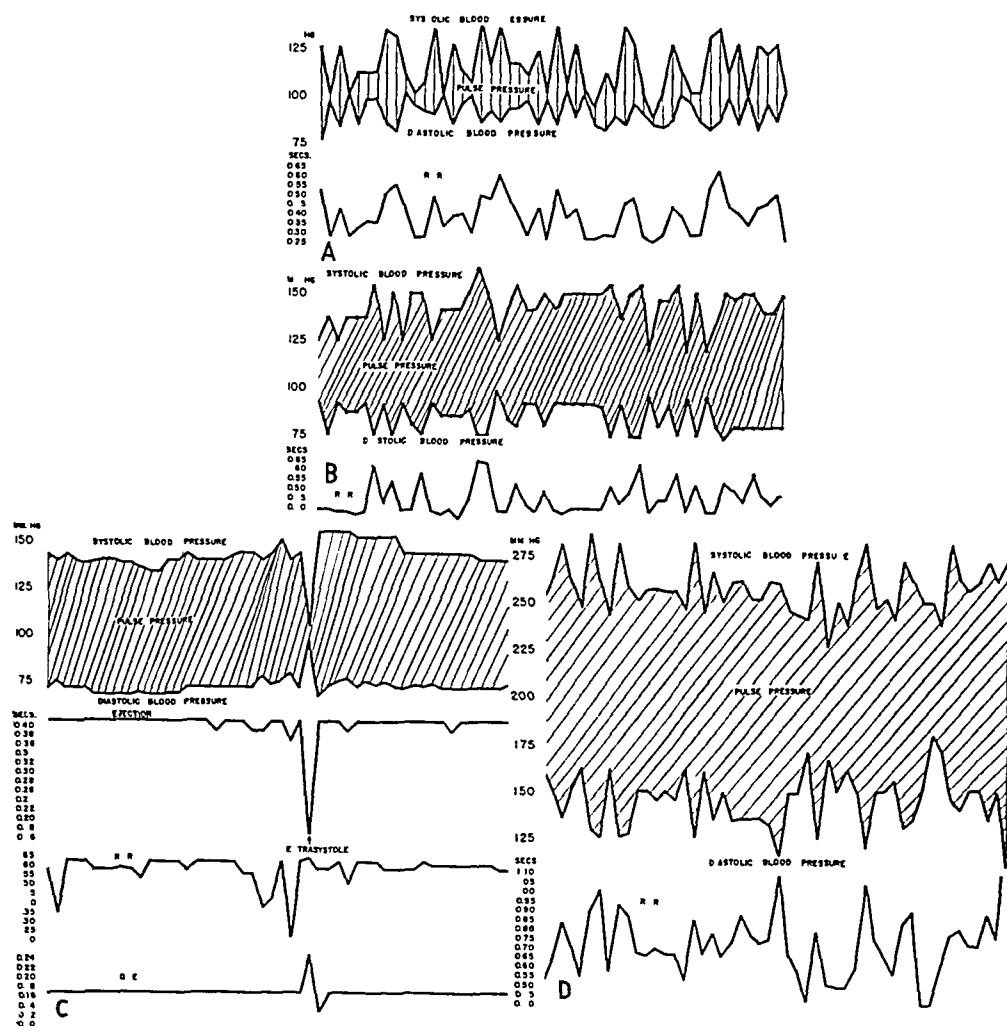


Fig 7—Charts constructed as in figure 5 and with the same conventions. Chart B is that of another patient, with auricular fibrillation and an average ventricular rate of 144 beats per minute. Chart C is that of a third patient, with auricular fibrillation and almost complete heart block, the average ventricular rate being 36 beats per minute. Chart D is that of a fourth patient, with auricular fibrillation and marked hypertension, the average ventricular rate being 90 beats per minute. In Chart C the time of occurrence of an extrasystole is indicated. Portions of the original curves for these patients are shown in B, C and D of figure 8. See text for discussion.

sure and 15 mm of diastolic pressure, but variations as great as 60 and 40 mm, respectively, being not infrequent. A definite relation is seen to exist between the cycle length and the levels of blood pressure, the

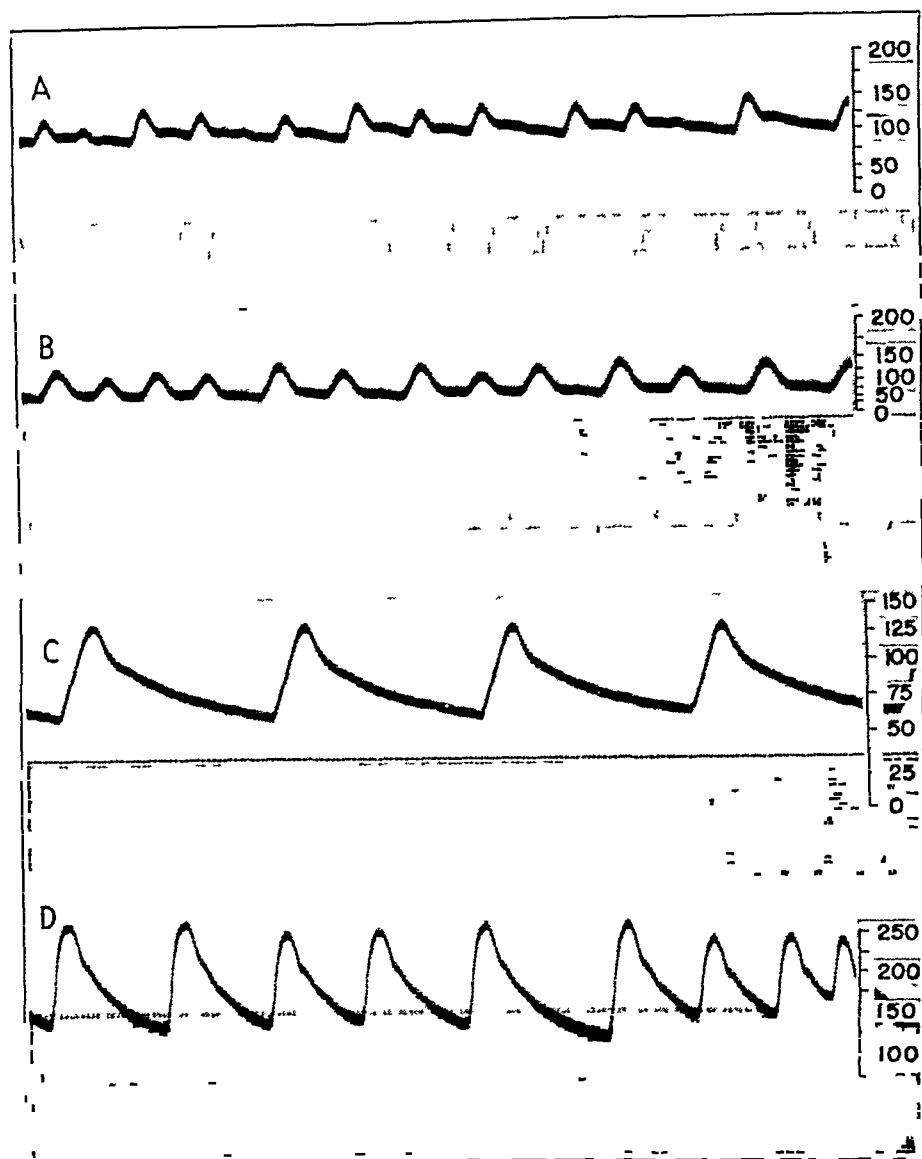


Fig 8—Portions of the original records (reduced) of 4 patients with auricular fibrillation. From the cases of the second, third and fourth of these the charts in figure 7 were constructed. The curves and conventions are as in figure 6, except that in *B* and *D* the electrocardiogram represents lead III.

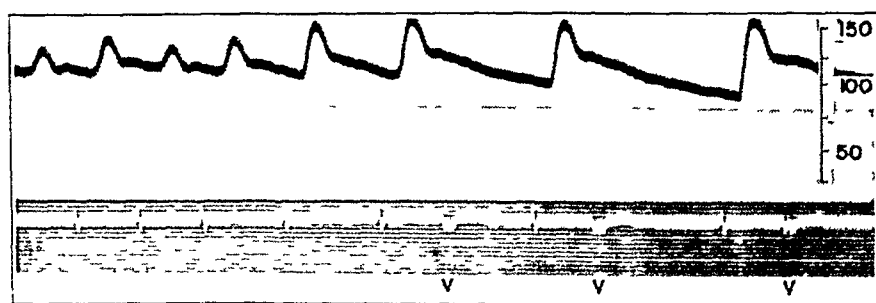


Fig 9—Portion of the original record (reduced) of a patient with auricular fibrillation and ventricular extrasystoles (*V*). The curves and conventions are as in figure 6. See text for discussion.

systolic blood pressure and pulse pressure bearing a direct relation to the preceding cycle, while the inverse holds for the diastolic pressure

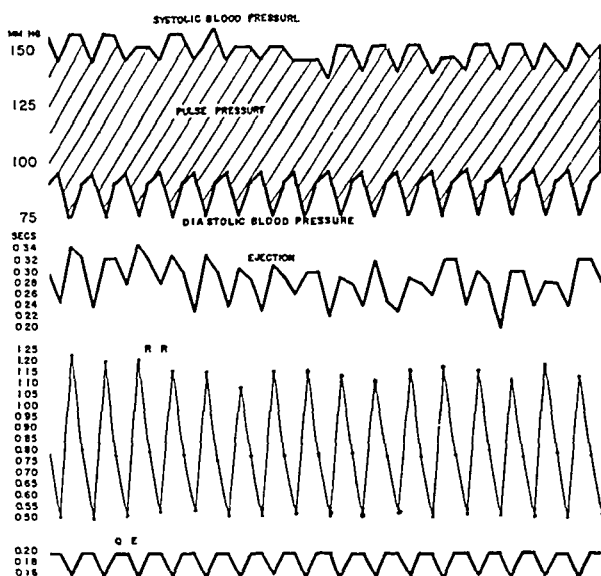


Fig 10—Chart constructed as in figure 5 and with the same conventions in the case of a patient with sinus rhythm and a persistent pulsus trigeminus due to a regularly recurring auricular extrasystole from the same focus, a portion of the original curve is shown in figure 11 *A*. See text for discussion

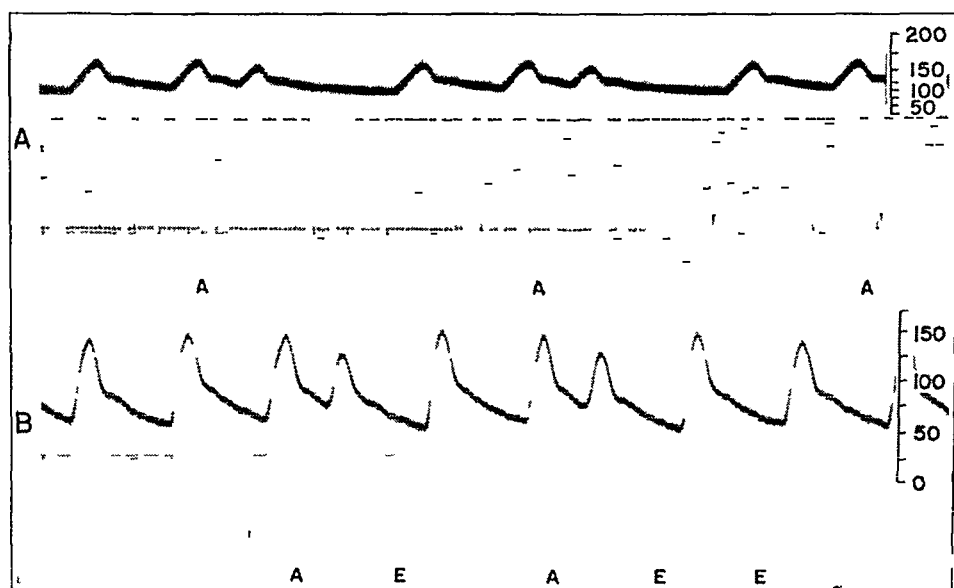


Fig 11—Portions of the original records (reduced) of 2 patients with sinus rhythm and auricular extrasystoles (*A*). The curves and conventions are as in figure 10. Record *A* is that of the patient on whom data are charted in figure 10. Record *B* is that of another patient with sinus rhythm and auricular extrasystoles showing aberrant conduction (*A*) and nodal escapes (*E*). See text for discussion

This correlation can be seen more clearly from the graphs (figs 2 and 3) in which these variables from 1 case, namely, systolic pressure, diastolic pressure and pulse pressure, are plotted for each of 50 successive beats against cycle length and against the duration of the diastole preceding the points used. Examination of these figures shows that the relation is not proportional, the relative amount of change being less marked with the longer cycles (diastoles) than with the shorter ones.

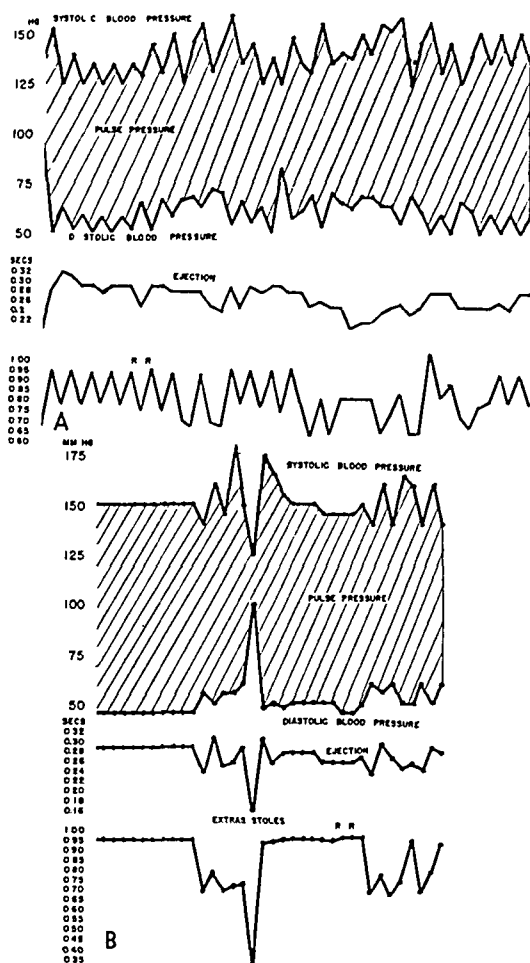


Fig 12—Charts constructed as in figure 5, with the same conventions, in the case of a patient with chronic auricular flutter. Portions of the original curves for this patient are shown in figure 13. The record in chart *A* was taken during a time when the auriculoventricular conduction was irregular, leading to irregular ventricular beating. That in chart *B* was taken during a period of regular auriculoventricular conduction interrupted by extrasystoles (as indicated) and followed by a final period of irregular ventricular beating. See text for discussion.

The duration of ejection, in all instances, was found to fit the square root formula ($S = K \sqrt{C}$) relating it to the cycle length. In the 4 cases in which the range of the cycle lengths was sufficiently great, K was found to be 0.23, 0.26, 0.26 and 0.26, respectively. In 1 of the latter,

150 beats were plotted (cf fig 4), obtained at three stages of heart failure, showing that the ventricular rate was the dominant factor in determining the duration of ejection

In this last case, records taken at intervals as the patient recovered from heart failure and reestablished her preexisting hypertensive level gave us the opportunity to study all the aforementioned variables under these changing conditions. The correlations are clearly shown in figure 5 (*A*, *B* and *C*), which illustrates the pressures in successive beats and the duration of the intervals in the cardiac cycle from the records taken as she recovered from heart failure. It will be seen that her pulse pressure increased on the average as her heart failure lessened (cf fig 5, *A* and *B*), only to decrease again when her diastolic pressure had risen (cf fig 5, *B* and *C*). Obviously several factors operated in this patient to give this result: (1) the change in the contractile power of her heart, (2) the slowing of the heart rate and (3) the degree of distention of her arterial system. Slowing of the heart rate and improvement in the power of the heart might be expected to increase the pulse pressure. The decrease in pulse pressure in the third record must therefore be ascribed to the change in the diastolic blood pressure with its associated alteration in peripheral resistance and in resistance of the elastic reservoirs.⁸ In figure 6 a few beats from each of the original records are reproduced for comparison. These curves illustrate the wide variation in pressure from beat to beat and, together with the other data we obtained, establish the large variation of pressure levels occurring in the irregular ventricular action of auricular fibrillation or flutter.

The effect of the ventricular rate on the blood pressure is illustrated in figure 7 (*B*, *C* and *D*). The diastolic pressure levels are approximately the same in all 3 cases, nevertheless, the systolic and pulse pressures show a remarkable variation. The difference in the average rate between *B* and *C* is only 27 beats per minute, and yet there is a striking reduction in systolic and pulse pressure at the faster rate. This is in contrast with the small difference in systolic and pulse pressure between *C* and *D*, despite the fact that the difference in rate is 108 per minute, or four times that between *B* and *C*. This tends to show that the variations in these pressure levels found in single patients apply also to the variations between different patients. Portions of the original curves are shown in figure 8.

The effect of regularity of action of the heart in removing the fluctuations in blood pressure is clearly shown in figure 7 *C*, in which, aside from the time when an extrasystole occurred, the pressures are seen to

⁸ Wiggers, C. J. Dynamics of Hypertension, *Am Heart J* **16** 515 (Nov) 1938

be practically constant. The influence of the state of the elastic reservoirs (the aorta and the large arteries) on the pulse pressure is shown by comparing figure 7 *D* with figure 5 *C*.

That the influence of a short cycle length produced by extrasystoles is similar to that noted in auricular fibrillation is shown in figure 7 *C*, in which the premature beat with the reduced filling period preceding it is associated, as might be expected, with a rise in diastolic pressure and a fall in systolic and pulse pressure. However, the changes caused by the extrasystoles are too great to be explained only on this basis, they must be partly attributed to the less synergic contraction of the various elements in the left ventricle. This is shown further in figure 9, which illustrates a case in which extrasystoles (*V*) occurring no more pre-

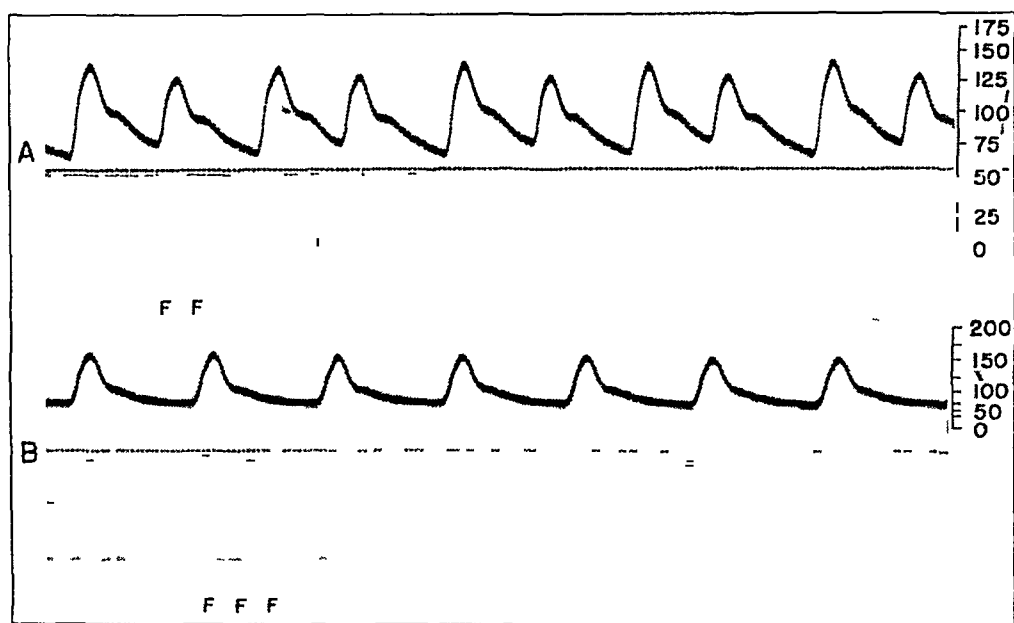


Fig. 13—Portion of the original record (reduced) of the patient on whom data are charted in figure 12. The curves and conventions are as in figure 6, except that in *A* the electrocardiogram represents lead III. Record *A* represents a period of irregular ventricular beating, record *B*, a period of regular beating. *F* represents the auricular flutter waves.

maturely than some of the beats conducted through the auriculoventricular junctional tissue (second and third beats of the record) failed to open the semilunar valves and had no appreciable influence on the pulse curve. More careful analysis of our data has shown that influences similar to this but much less striking occur even among the conducted ventricular beats in auricular fibrillation (cf. fig. 8 *A*).

This influence of extrasystoles is clearly shown by the rhythmic variations in all the variables observed in a case in which persistent pulsus trigeminus (fig. 10) was present, the extrasystoles being auricular

in origin (cf fig 11 *A*) In figure 11 *B* is shown a portion of the record of another case, with auricular extrasystoles (*A*) having aberrant conduction and followed by nodal escapes (*E*)

The influence of regularity of the ventricular beating on these variables is clearly illustrated in the records obtained on the patient with auricular flutter Figure 12 *A* shows the chart recorded during a period of continuously irregular ventricular beating in this patient, this resembles the changes noted in our cases with auricular fibrillation Figure 12 *B* shows the constancy of values for blood pressure in a graphic repre-

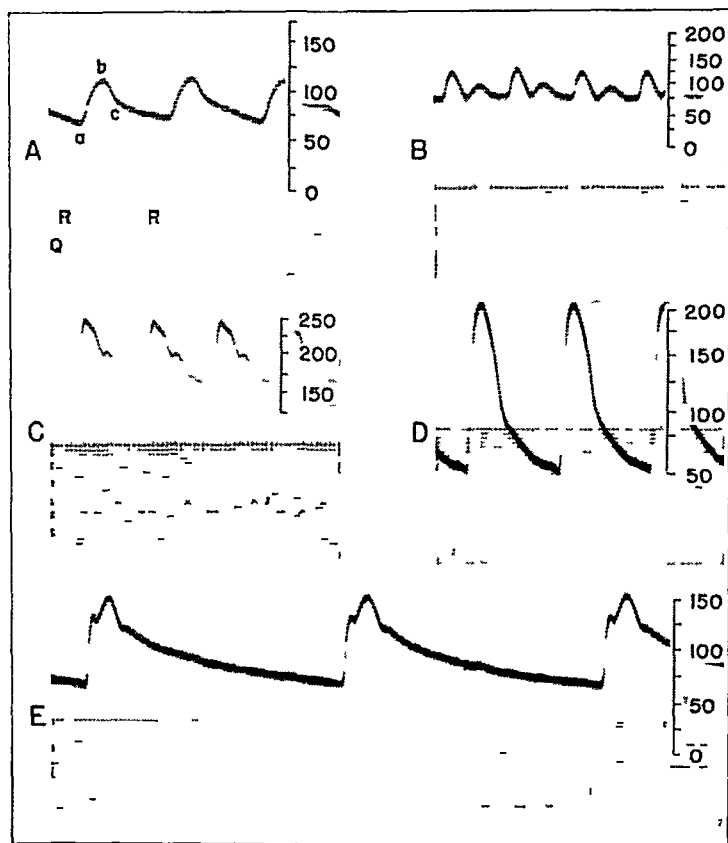


Fig 14—Portions of the original records (reduced) of 5 patients with sinus rhythm Record *A* shows normal regular rhythm in a patient without cardiovascular disease Record *B* shows sinus tachycardia in a patient with rheumatic heart disease Record *C* shows sinus rhythm in a patient with essential hypertension Record *D* shows sinus rhythm in a patient with a relatively free aortic valvular insufficiency of syphilitic origin Record *E* shows a sinus rhythm and a slow idioventricular rhythm at a rate of 20 in a patient with complete auriculoventricular block on an arteriosclerotic basis See text for discussion

sentation of 50 successive beats in this case of flutter when the ventricular rate was regular Fluctuations of blood pressure appeared only when this regularity was interrupted by extrasystoles (middle of curve) and by the development of irregular auriculoventricular conduction toward the

end of the record Figure 13 illustrates portions of the original curves obtained in the case of this patient (*A*) with and (*B*) without irregular ventricular beating

Figure 14 shows examples of the sort of records obtained with regular sinus rhythm (*A*) of normal sinus rhythm in a patient without cardiovascular disease, (*B*) of sinus tachycardia in a patient with rheumatic heart disease, (*C*) of sinus rhythm in a patient with essential hypertension, (*D*) of sinus rhythm in a patient with a relatively free aortic valve insufficiency of syphilitic origin, and (*E*) of a sinus rhythm and a slow idioventricular rhythm at a rate of 20 in a patient with complete auriculoventricular block on an arteriosclerotic basis These records again illustrate the constancy of blood pressure levels with regular beating of the ventricles, such as occurred in patients with auricular flutter and fibrillation when the ventricular rhythm was regular

COMMENT

Systolic, Diastolic and Pulse Pressure—The results on the variation in blood pressure are in close agreement with those obtained by Wiggers⁹ in experiments on the dog The differences in pulse pressure also agree with the variations in pulse amplitude reported by Katz and Feil⁷ and lend support to the view that pulse amplitude is determined by pulse pressure

Comparisons of either successive beats for individual patients or records for various patients indicate that the duration of the preceding cardiac cycle (and particularly the period of diastole, when the left ventricle can fill) is the most important factor governing the pressure levels This relation with the systolic and pulse pressure is a direct one, and with the diastolic pressure, an inverse one The effect of cycle length and filling time is not equal for equal increments at slow and rapid heart rates A change in their duration when the heart rate is rapid has a much greater influence than a similar change when the heart rate is slower This is in accord with the dynamics of filling of the ventricles as demonstrated by Wiggers and Katz¹⁰ and would indicate that a similar pattern of filling actually occurs in man Sufficient evidence has been presented to show that other influences appear to operate in cases of auricular fibrillation, as is shown by the wide scatter of systolic and pulse pressure at a given cycle length Among these must be considered the manner of summation of the fractionate contractions¹¹

9 Wiggers, C J Studies on the Pathological Physiology of the Heart The Intra-Auricular, Intraventricular, and Aortic Pressure Curves in Auricular Fibrillation, *Arch Int Med* **15** 77 (Jan) 1915

10 Wiggers, C J, and Katz, L N The Contour of the Ventricular Volume Curves Under Different Conditions, *Am J Physiol* **58** 439 (Jan) 1922

11 Wiggers, C J The Muscular Reactions of the Mammalian Ventricles to Artificial Surface Stimuli, *Am J Physiol* **73** 346 (July) 1925

from beat to beat. Evidence for this last factor may be found also in the variation in contour and duration of the QRS complex in the presence of auricular fibrillation, especially at rapid rates. That such a factor could operate is supported by the results found with ventricular extrasystoles, with which an unexpected small pulse pressure and low systolic pressure—up to the points where the valves are not even opened—are found at cycle lengths at which other beats were more effective (cf fig 9). This has also been found to apply to experimental extrasystoles.¹¹

The inverse relation of diastolic pressure to cycle length is to be expected, since the emptying of the elastic reservoirs into the small terminal arterioles and capillaries occurs during diastole. Variations in the relation might be expected on the basis that the central arteries are not filled to an equal extent at every systole. Such variations do occur, as can be seen by a casual inspection of the pressure curves. In short, the level of fulness of the central arteries as expressed by the pressure at the beginning of diastole is determined by what has happened during a number of preceding cycles.⁹

Obviously other factors, like respiration and reflex fluctuations in peripheral vasoconstriction, play an additional role in determining the levels of all of these pressures. For example, in figure 5 *A* a progressive rise in the general pressure levels, presumably due to peripheral vasoconstriction, was observed.

Our study has also shown that the properties of the elastic reservoirs (the aorta and the large central arteries) play a large role in cases of auricular fibrillation, as in cases of sinus rhythm,⁸ in determining the systolic and pulse pressure values.

Pulse Wave Contour—Not only the level of pressure but the pulse contour is altered by the cycle length. After all, the systolic and diastolic pressures represent only two points on the pressure curve and obviously do not give all the information obtainable from the entire curve. This is in accord with what has been observed in experimental animals,⁹ and the causes are presumably the same. It is important to emphasize that the position of the maximum systolic pressure occurs at different times in systole and that its value relative to the end systolic pressure is variable. The shorter the cycle length, the greater is the tendency for the pulse to become smoother, to have its summit earlier and to have the closure of the semilunar valves at a lower level relative to the summit.

Duration of Ejection—One of the variables which we have analyzed is the time occupied by ejection. In this we have confirmed the observa-

tions of Wiggers and Katz ¹² and Katz ¹³ on experimental animals and of Katz and Feil ⁷ on man. Our results show that the formula $S = K \sqrt{C}$ (when S equals the period of ejection, C equals the cycle length and K is a constant) predicts reasonably the duration of the period of ejection, and the constant, which we found to be about 0.26, agrees fairly well with that obtained by these authors. The scatter from this predicted formula is not unexpected, considering that other factors also operate to determine the filling and emptying of the left ventricle. We have confirmed the established fact that the primary change which occurs with a changing heart rate and cycle length is in the diastolic period.

QE Interval—The QE interval is determined by several factors ¹⁴. On the one hand, it is altered by the duration of the isometric contraction period which occupies the first period of systole before ejection begins and which has been shown to vary directly with the level of the diastolic pressure preceding ejection ⁷, it would be expected, therefore, to shorten the QE interval at the longer cycle length. On the other hand, the QE interval is also determined by the time it takes for the pulse to travel from the root of the aorta to the brachial artery, where the record of the pulse is taken. The evidence is clear ¹⁵ that the velocity of the pulse wave, which determines the time required to reach the brachial artery, is an inverse function of the diastolic pressure level, the lower the diastolic pressure, the slower is the pulse wave velocity. An examination of our data will show that the former factor is the dominant one, since a clear, though not consistent, tendency exists for the QE interval to be shortest when the diastolic pressure is lowest, namely, at the longest cycle length.

Implication of This Study—This study has demonstrated that the blood pressure in cases of auricular fibrillation is variable in successive beats and that this variability is determined by the irregularity in the beating of the ventricle. It disappears when the beats become regular and is aggravated when extrasystoles are superimposed. The fluctuation of blood pressure becomes more pronounced the greater the arrhythmia of the ventricle. The faster the average ventricular rate, the greater the variability at a given degree of ventricular arrhythmia.

12 Wiggers, C. J., and Katz, L. N. Specific Influence of the Accelerator Nerves on Duration of Ventricular Systole, *Am J Physiol* **53** 49 (Aug.) 1920.

13 Katz, L. N. Factors Modifying the Duration of Ventricular Systole, *J Lab & Clin Med* **6** 291-311 (March) 1921.

14 Katz, L. N., Landt, H., and Bohning, A. The Delay in the Onset of Ejection of the Left Ventricle in Bundle Branch Block, *Am Heart J* **10** 681 (July) 1935.

15 Wiggers, C. J. Physical and Physiological Aspects of Arteriosclerosis and Hypertension, *Ann Int Med* **6** 12 (July) 1932. Bazett, H. C., and Dreyer, N. B. Measurements of Pulse Wave Velocity, *Am J Physiol* **63** 94 (Dec) 1922.

Our observations incline us to the view that blood pressure in patients with auricular fibrillation having irregular beating of the heart cannot be determined by ordinary clinical means with any degree of accuracy. Our implication is not that the existence of hypertension or of the large pulse pressure in free aortic regurgitation cannot be ascertained in patients with this arrhythmia but that a more precise definition of the pressure values is subject to considerable error. The slower the ventricular rate and the less irregular its beating, the more precisely can these pressure values be defined. It is our belief from our study that the more laborious statistical methods of obtaining systolic blood pressure are probably no better than the ordinary means employed, at least, they do not justify the effort involved. For ordinary purposes the clinician must recognize the crudity of his determination, and when it is imperative to determine the pressure more precisely, which is rare, recourse may be had to a direct method, such as we have described.

SUMMARY

The blood pressure has been recorded in cases of auricular fibrillation in man by a direct method.

Fluctuations of blood pressure occur from beat to beat in cases of auricular fibrillation and other irregularities of the heart. The systolic and pulse pressure show a direct relation and the diastolic pressure an inverse relation to the preceding cycle length.

The Q-E interval was measured and found to shorten with the longer cycle lengths.

The duration of ejection fits the formula $S = K \sqrt{C}$, and in 4 of our cases in which a curve of means could be drawn K equaled 0.26, 0.26, 0.26 and 0.23.

In cases of auricular fibrillation and flutter with regular rhythm the values for blood pressure are nearly constant.

Extrasystoles are found to obey the same relation to the preceding cycle length as that found with auricular fibrillation and flutter, but in their presence additional factors play some role.

These results confirm and extend results obtained with the experimental animal and those in man based on accurate recording of the pulse. They indicate that pulse pressure determines pulse amplitude and that pulse contour is a mirror of the variations in internal pressure during the cardiac cycle at the site where the pulse is recorded.

Our results definitely show that it is impossible to obtain accurate determinations of blood pressure by any of the indirect methods when the pulse is grossly irregular.

Dr. Louis N. Katz furnished guidance in this study and advice in preparing the report. Mr. S. Rodbard gave technical assistance.

RENAL INVOLVEMENT IN DISSEMINATED LUPUS ERYTHEMATOSUS

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In recent years the disorder recognized as disseminated lupus erythematosus has become of increasing interest to internists and pathologists because of the widespread visceral and systemic involvement in the disease

The dermatologic classification of lupus erythematosus and the diversified clinical manifestations of the disseminated form have been reviewed in several recent articles and will not be repeated at length here. It is sufficient briefly to summarize.¹ In contradistinction to the more common or discoid form of lupus erythematosus, the disseminated type, recognized as early as 1845 by Hebra and Cazenave, was established as a grave disease by Kaposi² in 1872. In 1895 Sir William Osler³ stressed the importance of the systemic complications of a heterogeneous

Abridgment of thesis submitted by Dr. Stickney to the faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Medicine

1 Engman, M. F. Early Acute Lupus Erythematosus, *Arch Dermat & Syph* **35** 685-697 (April) 1937. Goeckerman, W. H. Lupus Erythematosus as a Systemic Disease, *J A M A* **80** 542-547 (Feb 24) 1923. Hissard, M. Le lupus erythémateux, *Paris méd* **1** 373-378 (April 29) 1933. Keil, H. Relationship Between Lupus Erythematosus and Tuberculosis. A Critical Review Based on Observations at Necropsy, *Arch Dermat & Syph* **28** 765-779 (Dec) 1933. Low, R. C., and Rutherford, A. Post-Mortem Report of a Case of Lupus Erythematosus, *Brit J Dermat* **32** 326-330 (Oct) 1920. Lyon, J. M. Acute Lupus Erythematosus, *Am J Dis Child* **45** 572-583 (March) 1933. Madden, J. F. Acute Disseminated Lupus Erythematosus, *Arch Dermat & Syph* **25** 854-875 (May) 1932. O'Leary, P. A. Disseminated Lupus Erythematosus, *Minnesota Med* **17** 637-644 (Nov) 1934. Pels, I. R. Review of Lupus Erythematosus Disseminatus, *Internat Clin* **4** 273-298 (Dec) 1933. Rose, E., and Pillsbury, D. M. Acute Disseminated Lupus Erythematosus—Systemic Disease, *Ann Int Med* **12** 951-963 (Jan) 1939. Roxburgh, A. C. Acute Disseminated Lupus Erythematosus. Five Fatal Cases, *Brit J Dermat* **45** 95-109 (March) 1933. Stokes, J. H. Case III. The Diagnosis of Disseminated Erythematosus Lupus, *M Clin North America* **10** 290-294 (Sept) 1926.

2 Kaposi, M. Neue Beiträge zur Kenntniss des Lupus erythematosus, *Arch f Dermat u Syph* **4** 36-78, 1872.

3 Osler, W. On the Visceral Complications of Erythema Exudativum Multiforme, *Am J M Sc* **110** 629-646 (Dec) 1895.

series of conditions called the erythema group. Some, but probably not all, of these were disseminated lupus erythematosus. In 1922 Ehrmann and Falkenstein⁴ were able to gather from the literature only 65 authentic cases in which there were necropsy records.

The disease occurs in the third and fourth decades, and the majority of patients are women. The role of tuberculosis as an etiologic factor has been fairly well disproved, but chronic infection of some type, frequently streptococcic, is important in the development of the disease. Exposure to light, mild injuries and irritants and allergy are considered to play an important part. The duration of the disease varies from a few weeks to several years. The prognosis is very poor. The initial signs may be cutaneous or systemic, and localized discoid lupus erythematosus may have been present for many years before dissemination takes place. Involvement of synovial and serous membranes and depression of bone marrow function with anemia, leukopenia, thrombopenia and abnormal leukocytes are common. There may be a generalized enlargement of the lymph nodes. Gastrointestinal symptoms and abdominal pain may necessitate a differentiation from a condition requiring surgical treatment. Endocarditis is frequently noted and has been extensively studied by Libman and Sacks,⁵ who have described a nonbacterial verrucous endocarditis. Bronchopneumonia is the usual terminal event. Clinical evidence of visceral damage is most commonly found in the urine. Albuminuria is almost always present at some time during the course of the disease, and with this there is usually a moderate number of erythrocytes and casts in the urine. These observations always lead to a consideration of the question of the presence of acute or chronic glomerulonephritis. Edema may be present, but it is usually limited to the regions of cutaneous involvement. There is rarely any rise in blood pressure.

It is the purpose of this study to analyze the renal findings, both clinical and at necropsy, in 15 patients with disseminated lupus erythematosus who came to autopsy at the Mayo Clinic between Jan 1, 1918 and July 1, 1939, inclusive. The diagnosis has been established in every instance histologically by biopsy or postmortem examination of the involved cutaneous regions according to the criteria of Goeckerman and Montgomery⁶ and clinically according to the diagnosis formulated by the Section on Dermatology and Syphilology of the American Medical Association.

4 Ehrmann, S., and Falkenstein, F. Ueber Lupus erythematosus, *Arch f Dermat u Syph* **141** 408-506 (Dec) 1922

5 Libman, E., and Sacks, B. A Hitherto Undescribed Form of Valvular and Mural Endocarditis, *Tr A Am Physicians* **38** 46-61, 1923

6 Goeckerman, W. H., and Montgomery, H. Lupus Erythematosus. An Evaluation of Histopathologic Examinations, *Arch Dermat & Syph* **25** 304-316 (Feb) 1932

The data derived from study at the Mayo Clinic of these patients and others not dying at the clinic are contained in a review by Montgomery⁷

The classification of these 15 patients, arranged according to O'Leary's criteria, is contained in table 1

Three illustrative cases will be treated in some detail, and the entire 15 will be summarized in tables 2 and 3

REPORT OF CASES

CASE 1—A woman first registered at the clinic in 1926, at the age of 23, because of a scaling eruption on both cheeks and behind one ear. The lesions were described as sharply defined, maculopapular and scaling, with slight infiltration and epithelial plugging. A diagnosis of early discoid lupus erythematosus was made. The results of a general examination were negative. The blood pressure was 120 mm of mercury systolic and 80 mm diastolic, the concentra-

TABLE 1—*Distribution According to Age of Fifteen Patients with Disseminated Lupus Erythematosus on Whom Necropsy was Performed*

Age, Years	Acute			Subacute	Generalized Discoid
	Total	Male	Female		
0-9	0	0	0	0	0
10-19	1	1	0	0	0
20-29	5	1	4	0	0
30-39	4	1	3	0	1 (male)
40-49	1	1	0	0	0
50-59	0	0	0	1 (female)	1 (female)
60-69	1	0	1	0	0
70-79	0	0	0	0	0
Total	12	4	8	1	2

tion of hemoglobin (Dare) was 76 per cent, and the leukocytes numbered 8,100 in each cubic millimeter of blood. The results of urinalysis were negative. The skin cleared under quinine therapy.

The patient was next seen on Dec 8, 1937, when she was 35 years old. She had been well until one year before, when the eruption on her face had returned. Late in the summer of 1937 she was sunburned. This exposure was followed by another flare-up of the eruption and by pain, swelling and stiffness in several joints.

The results of the general examination were essentially negative except for enlargement of the joints of the hands and dull red, raised areas with some scaling on the upper lip and over the hands and arms. The tonsils and one tooth were infected. The blood pressure was 115 systolic and 70 diastolic, the urine contained albumin, graded 2 on a basis of 1 to 4, and occasional erythrocytes, the blood urea was 30 mg per hundred cubic centimeters, and the urea clearance was 47.9 cc with a volume of 94 cc of urine. The hemoglobin measured 12.7 Gm. The erythrocytes numbered 4,000,000 and the leukocytes 5,000 in each cubic millimeter of blood. The sedimentation rate was 31 mm. The serum sulfates were 4.2 mg per hundred cubic centimeters. The diagnosis was as follows: subacute disseminated lupus erythematosus, chronic diffuse nephritis, chronic infectious arthritis. The patient was advised to have the teeth and tonsils cared for only after the cutaneous lesions had improved.

⁷ Montgomery, H. Unpublished data.

She returned home, and after the condition of the skin had improved somewhat, the tonsils were removed, in February 1938. She did very poorly after the tonsillectomy. Her throat remained sore, and the arthritis and the eruption became worse. New lesions appeared on her cheeks, forehead and neck.

She returned to the clinic on March 12, 1938. There were edema of the lips and cheeks and a maculopapular eruption on the forehead and neck. The temperature was 101 F and the blood pressure 98 systolic and 75 diastolic. On urinalysis the specific gravity was found to be 1.010, the albumin was graded 3, the erythrocytes were graded 1, and the hyaline casts were graded 1. The blood urea was 42 mg and the serum sulfates 67 mg per hundred cubic centimeters. The hemoglobin measured 9.7 Gm. The erythrocytes numbered 3,850,000, the leukocytes 4,400 and the platelets 112,000 in each cubic millimeter of blood. The diagnosis was acute disseminated lupus erythematosus. During the next seventeen days the patient went steadily downhill. The temperature remained elevated, the hemoglobin fell except immediately after a transfusion, and the leukocyte count fell steadily to 2,100 in each cubic millimeter of blood. The urinary albumin was graded 4, and hyaline casts and erythrocytes were present in most of the specimens of urine examined. The serum protein was 4.7 mg per hundred cubic centimeters. The urea rose to 202 mg per hundred cubic centimeters. Examination of the ocular fundi gave negative results except for a slight narrowing of the arterioles. Cultures of blood and urine were negative, 0.0014 mg of lead was present in 1 cc of urine. No evidence of tuberculosis could be found. Sulfanilamide up to 75 grains (4.9 Gm) per day was given, but the patient died on March 29, 1938 in a state of uremic coma.

At necropsy the anatomic diagnosis was as follows: lupus erythematosus, bronchopneumonia, anemia graded 2, fatty degeneration of the liver, abscess of the left kidney.

The kidneys together weighed 322 Gm. The external appearance was not significant except for small cysts, up to 0.8 mm in diameter. The cut surfaces were not abnormal. In the cortex of the left kidney there was an abscess measuring 4 by 5 mm. In sections stained for lipoids there were occasional lipid droplets in the epithelial cells of the convoluted tubules. In those stained with hematoxylin and eosin there were focal accumulations of lymphocytes and polymorphonuclear leukocytes in the cortical region. In the glomerular tufts there was an increase in the number of cells, with fewer erythrocytes than normal. In sections stained by the method of Mallory as modified by Heidenhain (fig 1) the cellular increase was seen to be endothelial, and many fibers of intracapillary connective tissue were present. The basement membrane was irregular and in many regions increased in thickness. There were no significant changes in the arterioles.

CASE 2—A woman, aged 22 years, was first admitted to the Mayo Clinic on June 1, 1929. Nine months before she had had an attack of diarrhea and vomiting, and a red eruption had appeared over the left cheek and about the eyelids. This spread to involve the other cheek and the bridge of the nose. Six months previously she had become jaundiced, with some pain in the right upper abdominal quadrant and light-colored stools. The jaundice cleared two weeks before admission, but the weakness and pallor became more marked. Shortly before admission, ultra-violet radiation was used on the skin, and this treatment was followed by a spread of the lesions to the neck, upper part of the chest, back, arms, elbows and fingers.

There was marked pallor with a slight icteric tinge. Over the whole precordium there was a systolic thrill with a loud systolic murmur over the apex but the heart was not enlarged. Both the spleen and the liver were easily palpated.

The face was covered with ill defined erythematous plaques to which adhered a fine scale that left keratotic plugs on removal. Over the rest of the body there were discrete and confluent papules and macules of a pink color with fine white scales. The temperature was 102 F. The patient was admitted directly to the hospital.

The blood pressure was 97 mm. of mercury systolic and 40 diastolic. The urine had a specific gravity of 1.010, it contained no albumin or casts but occasional erythrocytes. The concentration of hemoglobin (Dare) was 20 per cent, the erythrocytes numbered 990,000 and the leukocytes 7,200 in each cubic millimeter of blood. The fragility of the erythrocytes was normal, the serum bilirubin was 3.5 mg. per hundred cubic centimeters, and a blood smear showed 27 per cent lymphocytes and 25 per cent promyelocytes. A culture of the blood was negative. Agglutinations for *Brucella abortus* were negative. During the first two weeks the erythrocytes fell to 640,000, the hemoglobin to 15 per cent and the leukocytes



Fig 1 (case 1) —Heidenhain modification of Mallory stain ($\times 450$) Acute disseminated lupus erythematosus. Foci of increase in thickness of the basement membrane with fibers of intracapillary connective tissue, proliferation of endothelial cells in glomerular capillaries. Acute glomerulonephritis (Bell)

to 6,200. Because of the immaturity of many of the white cells, leukemia with skin manifestations was suspected, but a biopsy of the skin established a diagnosis of acute lupus erythematosus.

During the next month the patient was given bone marrow, fetal liver and roentgen ray treatments. The hemoglobin rose to 30 per cent, with 1,590,000 erythrocytes, and there were 3,600 leukocytes, with 32 per cent lymphocytes. In the urinalysis the albumin was graded 1 to 2. No casts or erythrocytes were seen. The skin gradually cleared and the patient improved, but by August 13 she began to get worse. There followed two transfusions, after which she improved. By September 4 the hemoglobin was 40 per cent, and the erythrocytes numbered 2,290,000, the platelets 250,000 and the leukocytes 6,800, with very few immature

cells For the first time, there was an increased fragility of the erythrocytes The blood urea was 27 mg per hundred cubic centimeters The cutaneous lesions showed only residual pigmentation

Soon after this there was a sudden turn for the worse An abscess of a tooth was followed by a generalized enlargement of the lymph nodes The leukocytes numbered 8,600 per cubic millimeter A severe reaction with fever, diarrhea and jaundice followed a transfusion The serum bilirubin rose to 14.6 mg, the urea to 52 mg per hundred cubic centimeters and the leukocytes to 11,000 per cubic millimeter The concentration of hemoglobin (Dare) fell to 15 per cent and the carbon dioxide-combining power to 15 per cent The patient died on Oct 3, 1929

At necropsy the anatomic diagnosis was as follows lupus erythematosus, splenomegaly (1,150 Gm), with infarcts, anemia and icterus, hypertrophy of the liver (2,168 Gm), terminal mitral vegetative endocarditis, fatty changes of the myocardium, iron pigmentation of the kidneys, lungs and lymph nodes

The kidneys together weighed 301 Gm There was nothing particularly abnormal in the gross appearance In sections of the kidney stained for lipoids and with hematoxylin and eosin, as well as in those stained by the method of Mallory with Heidenhain's modification, there were occasional lipoid droplets in the epithelium of the convoluted tubules Otherwise there were no significant changes Sections stained for iron contained pigmented particles in the convoluted tubules

CASE 3—A girl, aged 16 years, was first seen at the Mayo Clinic in November 1916 An abscess of the neck had been incised in 1914, and in the months preceding admission there had been an itching, papular, generalized cutaneous eruption The results of physical examination were negative except for the cutaneous lesions, for which a diagnosis of scabies was made The results of urinalysis were negative except for an occasional leukocyte

The patient was next seen on Sept 8, 1920 She had been easily exhausted and short of breath for about two years, and in April 1920 had had an attack of abdominal pain, fever and diarrhea, which her physician had considered typhoid fever With this there was some erythema of the face but no edema

The patient was an undernourished person, with thinned hair The ocular fundi were normal, the teeth and tonsils were infected The blood pressure was 120 mm of mercury systolic and 90 diastolic, and the temperature was 99 F The concentration of hemoglobin (Dare) was 60 per cent, the erythrocytes numbered 3,550,000 and the leukocytes 7,600 in each cubic millimeter of blood The Wassermann reaction was negative The specific gravity of the urine was 1.026, the albumin was graded 4, and there were occasional hyaline casts and erythrocytes The blood urea was 16 mg per hundred cubic centimeters, and the return of phenolsulfonphthalein was 45 per cent The diagnosis was chronic nephritis and acne rosacea

On Sept 20, 1920, tonsillectomy was performed Recovery was uneventful for three days, but on the fourth day the temperature rose to 104 F and the erythema of the face began to spread, to scale and to become edematous On October 8 the diagnosis of disseminated lupus erythematosus was established For the next four weeks the patient was under the care of the dermatologic and the nephritic service The blood pressure averaged 120 systolic and 60 diastolic The hemoglobin remained at 45 to 50 per cent, the erythrocytes varied from 2,700,000 to 3,700,000 and the leukocytes from 3,800 to 5,200 in each cubic millimeter of blood The Widal reaction was negative No tubercle bacilli were found in the urine, stools or sputum Cultures of the blood were negative A roentgenogram of the chest disclosed a lesion characteristic of tuberculosis in the upper lobe of the left lung

Five teeth were infected apically. The urine during this period always contained albumin graded 2 or 3, occasional hyaline casts and about 10 leukocytes per microscopic field. The specific gravity of the urine varied from 1 001 to 1 024 in dilution and concentration tests. The excretion of phenolsulfonphthalein in two hours was 60, 70 and 80 per cent in three tests. The blood urea varied from 16 to 30 mg and the creatinine from 1.2 to 1.3 mg per hundred cubic centimeters. The results of an examination of the ocular fundi were negative. The cutaneous lesions gradually cleared, and on Nov 6, 1920 the patient was sent home, on an anti-tuberculosis regimen.

She returned two months later because of a recurrence of the cutaneous lesions. At times since her dismissal there had been edema of the face and legs. On Jan 18, 1921 a radical alveolar resection of one molar was done. There was some exacerbation of the cutaneous lesions, but the temperature did not rise above 99 F. The blood urea was 34 mg per hundred cubic centimeters, the leukocytes numbered 5,200 in each cubic millimeter of blood, and the urine contained albumin graded 3 and granular casts. Results of tests of kidney function were essentially the same as on the previous admission. She improved and was sent home again.

On July 6, 1921 the patient was admitted for the fourth and last time. She had been well until May, when she had become ill with an infection of the upper part of the respiratory tract. In June she had had a constant fever and edema of most of the body. The physician she had consulted at home reported "cotton wool" exudates in the retina and a precordial friction rub. On admission her temperature was 101 F, and there was a persistent erythema of the face with lesions on the hips and hands. Rales were heard over the base of each lung. The heart sounds were distant, without murmurs. The blood pressure was 116 systolic and 84 diastolic. There was no edema of the skin. The ocular fundi showed two areas of recent "cotton wool" exudate without edema or hemorrhage. On July 11 an impacted tooth was extracted without much reaction. During July there was not much change in temperature or blood pressure. The urine contained albumin, hyaline and granular casts and erythrocytes in all specimens. The excretion of phenolsulfonphthalein was 45 per cent, and the blood urea rose from 29 to 50 mg per hundred cubic centimeters. The leukocytes rose from 5,200 to 9,400 in each cubic millimeter of blood. Cultures of the blood were negative, and the sputum contained no tubercle bacilli.

On August 6 an extensive bronchopneumonia developed, the patient rapidly became stuporous and died in convulsions on Aug 11, 1921. The blood urea rose to 162 mg per hundred cubic centimeters and the leukocytes to 11,600 in each cubic millimeter of blood the day before death.

At necropsy the anatomic diagnosis was as follows: disseminated lupus erythematosus, ulcerative tuberculous enteritis, caseating mesenteric lymph nodes containing tubercle bacilli, bilateral lobar pneumonia, bilateral fibrous pleuritis, miliary tuberculosis of the spleen.

The right kidney weighed 200 Gm. The external appearance was not significant, except that the markings were indistinct and the consistency was decreased. In sections of the kidney stained for lipid none was found. In those stained with hematoxylin and eosin there were small focal accumulations of lymphocytes in the cortex. The epithelium of the convoluted and straight tubules was flattened, and the tubules, which also contained hyaline casts, were dilated. The glomerular capillaries contained fewer erythrocytes than normal, and there was an increased amount of eosin-staining hyaline material. In sections stained by the Heidenhain modification of the Mallory method the basement membrane was very irregular.

and of about three times the normal thickness (fig 2) The endothelial cells were decreased in number, and there were many fibers in intracapillary connective tissue

The entire series of 15 cases is summarized in table 2

THE RENAL LESIONS

In summary, the clinical evidence of renal damage in these 15 cases is interesting In only 4 cases (1, 3, 4, 15) did the disease terminate in uremia, with a blood urea of more than 60 mg per hundred cubic centimeters In these and in 5 others (7, 9, 10, 11, 12) there were fairly constant albuminuria, microscopic hematuria and cylindruria In most instances there was a considerable fluctuation in the urinary findings,



Fig 2 (case 3) —Heidenhain modification of Mallory stain ($\times 525$) Acute disseminated lupus erythematosus Marked increase in thickness of the basement membrane, "wire loop" lesion as described by Baehr

which quite closely paralleled the severity of the cutaneous symptoms In 2 cases (2, 8) at no time was there more than slight albuminuria, and in 3 cases (5, 13, 14) there were no positive urinary findings All studies of renal function which were carried out indicated good function until the final stages of the disease In cases 4 and 15 albuminuria preceded the cutaneous lesions In the other cases cutaneous symptoms preceded the albuminuria, and the time which elapsed between the known onset of albuminuria and death varied up to eighteen months

In only 1 case (3) were there cotton wool exudates in the ocular fundi, and in 1 case (6) there were small hemorrhages In 3 others (1, 4, 5) there was evidence of angiospasm in the retinal arterioles

TABLE 2—Clinical Data in Fifteen Cases of Disseminated Lupus Erythematosus

Case	Age	Sex	Duration Dissemi- nation, Mo	Maximum Blood Pressure	Leukocytes per Cu Mm		Blood Urea, Mg per 100 Cc	Urine—1 4			Summary
					Range	Average		Albu- min	Red Blood Cells	Casts	
1	35	F	17	115/ 70	2,100 4,400	3,000	42 (202)*	4	2	2	Urea rose to 202 mg per 100 cc terminally, standard urea clearance 47.9 cc 3 months before death, blood culture negative
2	22	F	12	97/ 40	3,500 11,000	6,500	27 (52)*	1 2	0	0	Many remissions, jaundice, exacerbation fol- lowing ultraviolet light, anemia, marked lymphocyte immaturity
3	21	F	60	120/ 90	3,800 9,400	6,200	16 (162)*	3	2	2	Many remissions, terminal rise in urea, urine negative during remissions, "cotton wool" exudates in fundi, P S P + 45%, 60%, 70%, 80% on different occasions, active tubercu- losis of lungs
4	34	F	48	170/120	3 000 21,000	7,300	34 (126)*	3	3	1	Many remissions, albuminuria preceded cuta- neous symptoms, in fundus angiospasm of nephritic type, rise in urea only in last four days
5	24	F	1½	108/ 60	2,800 4,200	3,600		0	0	0	Joint symptoms, nine months pleural and pericardial effusion, marked anemia
6	62	F	6	120/ 70	6,100 8 800	6 900	28 (32)*	2	Occa- sional	0	Terminal hemiplegia, multiple emboli from thrombosis of iliac veins, in fundus hemor- rhage without exudate
7	34	M	10	125/ 75	6,000 12 000	7 000	16 (50)*	2	Occa- sional	1	Multiple joint involvement, many petechiae immature lymphocytes
8	21	F	9	120/ 76	2 200 5,800	3,700		1	Occa- sional	0	Remissions with negative urinary findings
9	31	F	9	154/ 82	4,100	4,100	16	1	2	0	Subacute bacterial endocarditis, blood culture, Streptococcus viridans
10	19	M	12	126/ 80	11,000 25 000	17 000	38	2	0	0	Exacerbation following roentgen treatment, many joint symptoms
11	27	M	3	130/ 50	2,700 4,900	3,600		2	0	0	Superimposed erythema multiforme, vegeta- tive endocarditis
12	40	M	2 weeks	132/ 64	2,700 12,000	6,300	30	2	0	1	Lobar pneumonia, skin always sensitive to light, low grade fever and loss of weight for six months
13	58	F	15	130/ 74	9,100 19,000	14,000		0	0	0	Died of pneumococcal meningitis
14	33	M	60	105/ 60	3,400 4,500	4 000		0	0	0	Operated on for acute condition of gallbladder
15	55	F	16 years	178/110	4,500 7,100	5,800	146	3	2	2	Albuminuria of twenty years' duration, chronic glomerulonephritis, cutaneous lesions inactive during terminal illness

* Terminal determination

† Excretion of phenolsulfonphthalein

Before the pathologic findings in the kidneys of this series are discussed it will be in point to review the pathologic reports in the literature

Brooke in 1895⁸ described the appearance of the kidneys of a woman aged 33 years as follows "The kidneys were enlarged with all the signs of soft white swelling The kidney lesions were obviously merely acute supervening complications" Sequeira and Balean⁹ in 1902 reported an autopsy as follows "The microscope showed a condition of glomerulotubular nephritis of a fairly acute type with a slight increase in the connective tissue The condition was not compatible with a nephritis of long standing such as would have been found had the affection dated back to the scarlet fever" (from which the patient had suffered six years before) Little¹⁰ and MacLeod¹¹ called attention to "nephritis" Short¹² in 1907 reported a case in which the kidneys were very pale and mottled There was "a chronic interstitial change in the epithelium with some glomerular tufts obliterated" There was also "hyaline thickening of the interlobular vessels" The 1 case in the series of Keith and Rowntree¹³ in which necropsy was performed is included in this series as case 3 Keefer and Felty¹⁴ in 1924 reported normal kidneys in 1 case (later revised by Jarcho¹⁵) and a chronic nephritis with fibrosis in another

Baehr, Klempeier and Schifrin¹⁶ reported 23 cases of disseminated lupus erythematosus in which necropsy was performed and found in 18 conspicuous glomerular changes, which they described as "proliferative

8 Brooke, H G Lupus Erythematosus and Tuberculosis, *Brit J Dermat* **7** 73-77 (Jan) 1895

9 Sequeira, J H, and Balean, H Lupus Erythematosus A Clinical Study of Seventy-One Cases, *Brit J Dermat* **14** 367-387 (Oct) 1902

10 Little, G A Case of Lupus Erythematosus, *Brit J Dermat* **17** 104 (March) 1905

11 MacLeod, J M H Case of Lupus Erythematosus, Associated with Nephritis, *Brit J Dermat* **20** 162-165 (May) 1908

12 Short, T S Fatal Cases of Acute Lupus Erythematosus, *Brit J Dermat* **19** 271-274 (Aug) 1907

13 Keith, N M, and Rowntree, L G A Study of the Renal Complications of Disseminated Lupus Erythematosus Report of Four Cases, *Tr A Am Physicians* **37** 487-502, 1922

14 Keefer, C S, and Felty, A R Acute Disseminated Lupus Erythematosus Report of Three Fatal Cases, *Bull Johns Hopkins Hosp* **35** 294-304 (Sept) 1924

15 Jarcho, S Lupus Erythematosus Associated with Visceral Vascular Lesions Series of Autopsied Cases, *Bull Johns Hopkins Hosp* **59** 262-273 (Oct) 1936

16 Baehr, G, Klempeier, P, and Schifrin, A A Diffuse Disease of the Peripheral Circulation, Usually Associated with Lupus Erythematosus and Endocarditis, *Tr A Am Physicians* **50** 139-155, 1935

and thrombotic lesions of the glomerular loops, sometimes involving only segments and at times generalized, superficially resembling subacute bacterial endocarditis, but the rest of the affected glomerulus was not normal." Baehr and his associates described a hyaline thickening of the capillary wall called "a wire loop lesion." They regarded it as entirely different from the hyaline degeneration seen in chronic glomerulonephritis. Jarcho, and Denzer and Blumenthal¹⁷ have confirmed these findings. In 1 of Jarcho's cases results of earlier examinations were reported as negative by Keefer and Felty.

Snapper¹⁸ has written a chapter in "The Kidney in Health and Disease" on renal involvement in disseminated lupus erythematosus. He described swelling of the glomeruli with proliferation and swelling of the loops and cloudy swelling of the glomerular capsule, as well as interstitial abscesses. Mook and his associates¹⁹ found 1 case in which the kidneys were of the primary contracted type, characteristic of hypertensive disease. Rose and Goldberg²⁰ reported a case with associated chronic arteriolar nephrosclerosis and another with "parenchymatous degeneration of the kidneys."

The pathologic findings in the present series are summarized in table 3. Histologic pictures of the kidneys in 4 cases are shown in figures 1, 2 and 3.

It will be noted that the weights of all the kidneys were normal or greater than normal, with a mean of 380 Gm (organs with congenital cystic disease excluded). There are 3 cases in which there was definite hypertrophy (4, 7, 9), and in none of these was there much interstitial edema. In 2 of the 15 cases there was also hypertrophy of the liver. The absence of any contraction of the kidneys is consistent with the fact that severe hypertension was not found in this series. Likewise, the absence of significant changes in the renal arteries and arterioles is consistent with the clinical observations. The degree of generalized arteriosclerosis, except in patients of middle age, was not graded more than 1 on a basis of 1 to 4. Small miliary abscesses, such as were found in cases 1, 3 and 4, frequently occur in toxic diseases. A typical pyelonephritis was not found.

17 Denzer, B. S., and Blumenthal, S. Acute Lupus Erythematosus Disseminatus, *Am J Dis Child* **53** 525-540 (Feb) 1937.

18 Snapper, I. Kidney Trouble in Acute Lupus Erythematosus, in Berglund, H., and Medes, G. The Kidney in Health and Disease, in Contributions by Eminent Authorities, Philadelphia, Lea & Febiger, 1935, pp 433-439.

19 Mook, W. H., Weiss, R. S., and Bromberg, L. K. Lupus Erythematosus Disseminatus, *Arch Dermat & Syph* **24** 786-829 (Nov) 1931.

20 Rose, E., and Goldberg, L. C. The Visceral Lesions of Acute Disseminated Lupus Erythematosus, *M Clin North America* **19** 333-346 (July) 1935.

The most common significant histologic observation was an increase in the number of endothelial cells of the glomerular tufts with a reduc-

TABLE 3—*Renal Changes Seen at Necropsy*

Case	Principal Cause of Death	Total Kidney Weight, Gm	Glomeruli	Epithelium of the Tubules	Comment
Acute disseminated lupus erythematosus					
1	Bronchopneumonia	322	Marked increase in endothelial cells, focal increase in thickness of basement membrane	Occasional lipid drop lets and hyaline casts	Focal interstitial lymphocytes and polymorphonuclear cells (fig 1)
2	Bronchopneumonia, anemia	301	Essentially normal	Occasional lipid drop lets	Terminal vegetative endocarditis, hypertrophy of liver, spleen
3	Miliary tuberculosis	200 (1 kidney)	Irregular thickened basement membrane, hyaline masses in capillaries	Slight atrophy of convoluted tubules	Moderate number of interstitial lymphocytes, "wire loop" capillaries of kidney (fig 2)
4	Bronchopneumonia, renal failure	485	Epithelial crescents in about 3%, occasional hyalinization	Focal regions of lipoids, hyaline casts, no marked atrophy	Hypertrophy of liver and heart, not typical chronic glomerulonephritis, multiple abscesses in both kidneys
5	Bronchopneumonia, anemia	292	Hyaline thrombi in capillaries, slight increase in thickness of basement membrane (fig 3A)	Granular casts	Amyloid not present
6	Infarct of brain	322	Essentially normal except infarction	Essentially normal	Multiple emboli and infarcts
7	Bronchopneumonia	710	Slight increase in endothelial cells	Hyaline casts	Changes nowhere marked
8	Bronchopneumonia, anemia	277	Hyaline granules in capillaries	Granular casts	Fatty changes in myocardium and liver
9	Rheumatic endocarditis	465	Essentially normal (fig 3B)	Hyaline and granular casts	Lesions characteristic of bacterial endocarditis not found in kidneys
10	Bronchopneumonia	1,000	Essentially normal except for cysts	Lipoid droplets in cystic regions	Bilateral congenital cysts of kidneys
11	Vegetative endocarditis	390	Slight increase in endothelial cells	Essentially normal	Low grade pyelonephritis
12	Lobar pneumonia	378	Slight increase in endothelial cells	Essentially normal	No marked changes
Subacute Disseminated Lupus Erythematosus					
13	Pneumococcal meningitis	260	Essentially normal	Occasional lipid	Arterial changes consistent with age 58
Generalized Discoid Lupus Erythematosus					
14	Miliary tuberculosis	In creased	Increase in endothelial cells	Essentially normal	"Large white kidneys"
15	Chronic glomerulonephritis	344	Hyalinization with many crescents	Atrophy with dilatation	Typical chronic glomerulonephritis

* Two kidneys present, only one kidney weighed

tion of the number of erythrocytes in the capillary loops. Some degree of proliferation of endothelial cells was present in 6 cases (1, 4, 7, 11, 12, 14). The presence of hyaline eosin-staining material in the glomerular capillaries, noted in 5 cases (1, 3, 4, 5, 8), probably represents a

degenerative process In 5 cases (1, 3, 4, 5, 12) there were definite fibers, which stained like and apparently derived from the basement membrane, seen within the glomerular capillaries in sections stained with



Fig 3—*A* (case 5), Heidenhain modification of Mallory stain ($\times 700$) Acute disseminated lupus erythematosus Hyaline masses in the glomerular capillaries entirely surrounded by basement membrane *B* (case 9), Heidenhain modification of Mallory stain ($\times 450$) Acute disseminated lupus erythematosus Essentially normal glomerulus, clinically as severe a cutaneous and systemic disease as any of the others

the azocarmine stain Bell²¹ has described such fibers in acute nephritis, and they will be discussed later Tubular damage, except in regions related to infarction, was minimal throughout, although a few hyaline and granular casts were found in several cases No significant deposit of lipoid was found, and there was no evidence of amyloidosis

The inclusion of cases 14 and 15 in this series may be questioned Both were instances of generalized discoid lupus erythematosus In case 14 the renal findings were insignificant, but in case 15 there was chronic glomerulonephritis The terminal events in the latter case were those of passive congestion and cardiac rather than renal failure It is uncertain how long the renal disease had existed, but in 1914, fifteen years before death, a note had been made that there had been "kidney disease for nine years" A lesion on the scalp had been present since 1908 Although the albuminuria was constant, hypertension was not known to exist before the final admission The cutaneous lesions were inactive during the terminal stages

In order to compare the changes just summarized with those in other types of disease, a group of patients whose ages fell within the range of those in this series was collected, included were most of the patients between 20 and 45 years of age from whom kidney tissue was available Eighty-five patients dying of various causes and coming to necropsy between Nov 1, 1937 and Oct 1, 1938 inclusive were selected By study of sections of the kidney 11 of these were found to have renal changes comparable to those in most of the patients in the lupus erythematosus series These changes are given in table 4, and these patients are referred to as the "control series"

The changes seen in most of the cases of disseminated lupus erythematosus are not similar to those seen in severe diseases of the kidney The kidneys in the control series, which did not include any with known renal disease, showed changes as marked as most of those seen in the lupus erythematosus series (fig 4), but the intracapillary hyaline changes were not seen in the control group

Bell,²¹ Dunn and McNee²² and Keith and Thomson²³ have described changes in acute nephritis similar to those seen in disseminated lupus erythematosus We refer to avascularity of the glomerulus, proliferation of the endothelial cells and irregularity of the basement membrane and presence of fibers within it In all their cases the disease was of

21 Bell, E T The Pathology and Pathogenesis of Clinical Acute Nephritis, *Am J Path* **13** 497-552 (July) 1937

22 Dunn, J S, and McNee, J W A Contribution to the Study of War Nephritis, *Brit M J* **2** 745-751 (Dec 8) 1917

23 Keith, N M, and Thomson, W W D War Nephritis A Clinical, Functional and Pathological Study, *J Urol* **3** 87-139 (June) 1919

short duration (a few days to three or four weeks), while in our cases of disseminated lupus erythematosus the average duration of the disease was sixteen and a half months and of the albuminuria six months

The peculiar intracapillary hyaline thrombosis seen in our cases is similar to the lesion seen frequently in bacterial endocarditis and described by Lohlein,²⁴ Baehr²⁵ and Bell²⁶ Its nature has led to much

TABLE 4—"Control Series" of Eighty-Five Patients Between Ages Twenty and Forty-Five

Sex	Age	Cause of Death	Duration	Blood Urea, Mg in 100 Cc	Urine, Grade			Kidney Weight Gm	Microscopic Changes in Kidneys
					Albu min	Eryth ro Casts	cytes		
M	25	Chronic ulcerative colitis with peritonitis	2 months	14	2	0	1	323	Increased endothelial cells with intracapillary fibers (fig 4)
F	39	Staphylococcal septicemia	7 days	166	1	0	0	493	Irregular basement membrane increase in endothelial cells
F	39	Fibroid uterus with peritonitis	2 weeks	32	2	2	3	267	Increase in endothelial cells
F	32	Brain tumor	10 days	26	0	0	0	234	Increase in endothelial cells
M	27	Chronic encephalitis	10 days	34	0	0	0	242	Increase in endothelial cells
M	33	Lobar pneumonia	10 days	*	2	2	2	241	Intracapillary fibers, increase in endothelial cells
F	42	Gangrene of colon	*	60	2	1	1	265	Increase in endothelial cells
F	35	Mitral endocarditis, cardiac decompensation	2 months	24	4	0	0	337	Increase in endothelial cells, infarction
M	22	Peritonitis	2 months	20	3	1	1	290	Increase in endothelial cells, intracapillary fibers
M	22	Chronic empyema	*	*	2	0	0	413	Increase in endothelial cells
F	38	Cirrhosis of liver	1 year	28	3	0	0	415	Increase in endothelial cells

* Unknown

discussion Bell expressed the belief that it comes from the lodgment of bacteria, but neither clinically nor pathologically has this theory been proved In none of the present cases in which this lesion existed was an

24 Lohlein, M Ueber hamorrhagische Nierenaffektionen bei chronischer ulzeröser Endokarditis (Embolische nichteitrige Herdnephritis), *Med Klin* **1** 375-379 (March 6) 1910

25 Baehr, G The Significance of the Embolic Glomerular Lesions of Subacute Streptococcus Endocarditis, *Arch Int Med* **27** 262-264 (Feb) 1921

26 Bell, E T Glomerular Lesions Associated with Endocarditis, *Am J Path* **8** 639-664 (Nov) 1932

organism cultured except by Welsh,²⁷ as mentioned in the case reports. Lohlein and Baehr expressed the opinion that the presence of bacteria can be demonstrated often enough to prove the hypothesis of bacterial origin in cases of bacterial endocarditis, but Baehr did not consider the lesion of disseminated lupus erythematosus to be similar to that of bacterial endocarditis. In the former disease all parts of the glomerulus are involved, while in the latter only a portion of the glomerulus is affected, according to Baehr.

If in disseminated lupus erythematosus the renal disorder we are dealing with is an acute glomerulonephritis, it must be concluded that the process is not of a duration coinciding with that of the albuminuria.

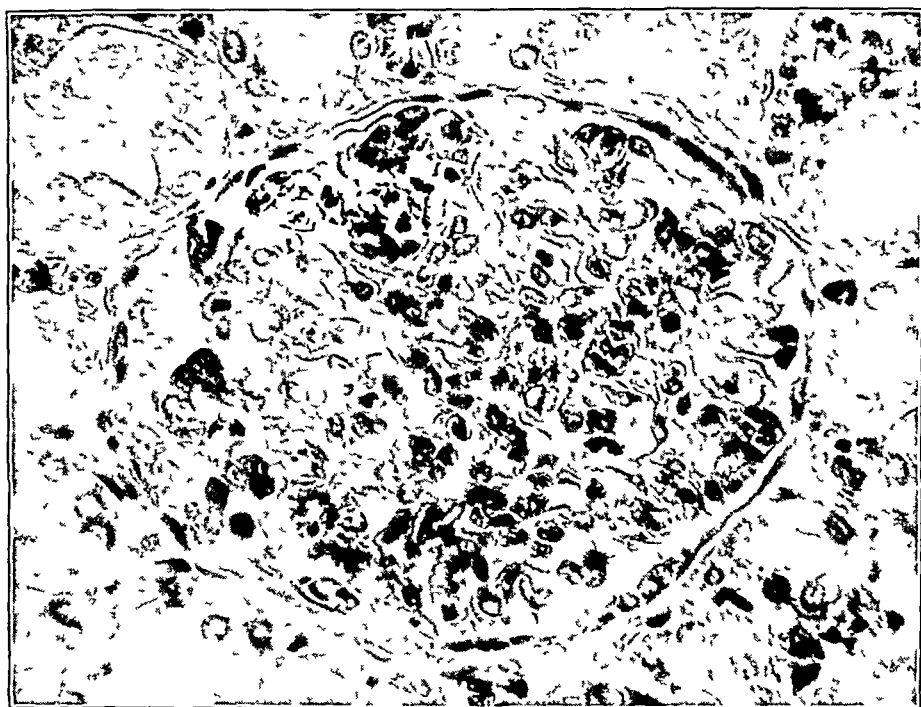


Fig 4 (case 1) —Control series. Heidenhain modification of Mallory stain ($\times 450$). Death from chronic ulcerative colitis with generalized peritonitis, changes similar to those in figure 1, proliferation of the endothelial cells of the glomerular capillaries with intracapillary fibers.

and hematuria but that it is a terminal process. The other possibilities which might be considered are that the disorder is a peculiar variety of nephritis with a low grade of virulence or that it is a degenerative process secondary to a toxic debilitating disease. Mallory, in the discussion of Cabot²⁸ case 24201, expressed the opinion that the renal

27 Welsh, A. L. Specificity of a *Streptococcus* Isolated from Patients with Pemphigus. Preliminary Report, *Arch Dermat & Syph* **30** 611-630 (Nov) 1934.

28 Acute Disseminated Lupus Erythematosus, Cabot Case 24201, *New England J Med* **218** 838-843 (May 19) 1938.

changes are not primary. The albuminuria of lupus erythematosus is not as constant or as severe as that seen in acute and chronic glomerulonephritis.

The relationship of the pathologic characteristics of the kidneys as described in preceding paragraphs to those of the cutaneous lesions in disseminated lupus erythematosus raises several interesting questions. Goeckerman and Montgomery have summarized what is commonly accepted as the histologic picture of the lesions. They emphasized dilatation of the capillaries and lymphatics, perivascular polymorphonuclear and lymphocytic infiltration, hyperkeratosis and edema of the cutis. They referred to the absence of proliferative vascular changes, but this Montgomery²⁹ has described as a change great enough to cause an obliteration of the smaller vessels. There is some thickening of the arterioles due to a mild proliferation of the endothelium and to edema, but there is no obliteration or organization. Hyaline changes are not seen.

In the kidneys the accumulations of lymphocytes, when present, are focal rather than perivascular. The endothelial proliferation is likewise never enough to cause obliteration of the vessels.

It may be of interest to mention a few of the observations made on hearts in this series of cases. Endocarditis in disseminated lupus erythematosus has been reported as a frequent occurrence by Weidman and Gilman³⁰. Libman and Sacks described an atypical verrucous endocarditis, characterized by a fibrinous pericarditis and a valvular and mural endocarditis with small vegetations at the line of closure of any of the valves. No Aschoff bodies could be found. Baehr and his associates found that in 13 of their 23 cases there was associated non-rheumatic verrucous endocarditis, which in 5 instances extended to the mural endocardium. In our series there were 3 patients with endocarditis. From the blood of 1 patient *Streptococcus viridans* was cultured. From the other 2 patients evidence of bacterial origin of the endocarditis was not obtained, but the vegetations did not extend onto the mural endocardium.

SUMMARY

The visceral involvement in disseminated lupus erythematosus has been reviewed clinically. The pathologic changes in the kidneys in 15 fatal cases have been studied.

In 8 of the 15 cases there was no definite renal change except that seen terminally in debilitating disease.

²⁹ Montgomery, H. Personal communication to the authors.

³⁰ Weidman, F. D., and Gilman, R. L. A Case of Acute Disseminated Lupus Erythematosus. Necropsy Disclosing Acute Endocarditis, but not Tuberculosis, *Brit J Dermat* **43** 641-647 (Dec.) 1931.

Without exception, the weight of the kidneys was normal or greater than normal. No contracted kidneys were found.

The most definite lesion was a proliferation of the endothelial cells of the glomerular capillaries. Hyaline thickening of these capillary walls and an irregularity and thickening of the basement membrane were also frequently present. These changes are somewhat similar to those which have been described in acute glomerulonephritis and the toxemias of pregnancy.

In 1 case in this series (case 15) there were pathologic changes characteristic of glomerulonephritis. The relationship of the changes noted to the lupus erythematosus is uncertain, since the renal disease preceded the cutaneous and the cutaneous lesions were inactive during the final illness.

In 1 other instance (case 4) there was some evidence of a subacute or early chronic glomerulonephritis. In this patient, too, the evidence of renal damage was known to have antedated the onset of the cutaneous lesions.

The arteries and arterioles were normal in most of the cases. In several there was slight thickening of the intima, but no thromboses were seen.

The changes in the tubules were of a minor nature.

CONCLUSIONS

A common distinct renal lesion does not exist.

Clinically, the duration of renal abnormality is much longer than the pathologic change would indicate, therefore, the disease either is not an ordinary glomerulonephritis or is of low virulence with slow progression. Probably the changes are secondary to toxic processes and do not represent primary renal disease. Similar changes were noted in the control group. The coincidence of cutaneous and renal exacerbations might lead to the conclusion that the pathologic findings were merely those of the recent terminal stage and that the previous renal flare-ups had subsided without scar. Even if this is true, the clinical history of the final stage is still longer than that of the usual acute glomerulonephritis.

MEASUREMENT OF VITAMIN A STATUS OF YOUNG ADULTS BY THE DARK ADAPTATION TECHNIC

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LOS ANGELES

With the recognition that cases of mild, subclinical vitamin deficiency are much more common than cases of severe deficiency, the need for adequate diagnostic methods for early avitaminotic states is urgently felt by clinicians. Only by such methods can the clinician determine the borderline states of malnutrition that not only contribute to his patients' ill health but prevent the best response to therapeutic measures.

As a criterion of deficiency of vitamin A, the night blindness or dark adaptation test is valuable, especially since the work of Wald,¹ Wald and Clark,² Hecht and his co-workers³ and others has demonstrated the physiologic role of vitamin A in the generation of the visual purple. Impairment of the visual cycle occurs as one of the first signs of an inadequate supply of vitamin A.

Jegheers⁴ has reviewed the literature on this test, and Hecht⁵ has reviewed the literature on rods, cones and the chemical basis of vision. Studies by various workers with different instruments include those of Jeans and Zentmire,⁶ Jeans, Blanchard and Zentmire,⁷ Edmund and Clemmesen⁸ and Hecht and Mandelbaum.⁹

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1 Wald, G. Carotenoids and the Visual Cycle, *J Gen Physiol* **19** 351, 1935

2 Wald, G., and Clark, A. Visual Adaptation and Chemistry of the Rods, *J Gen Physiol* **21** 93, 1937

3 Hecht, S., Chase, A. M., Schlaer, S., and Harg, C. The Regeneration of Visual Purple in Solution, *Science* **84** 331, 1936

4 Jegheers, H. Night Blindness as a Criterion of Vitamin A Deficiency. Review of Literature with Preliminary Observations of Degree and Prevalence of Vitamin A Deficiency Among Adults in Both Health and Disease, *Ann Int Med* **10** 1304, 1937

5 Hecht, S. Rods, Cones and the Chemical Basis of Vision, *Physiol Rev* **17** 239, 1937

6 Jeans, P. C., and Zentmire, Z. A Clinical Method for Determining Moderate Degrees of Vitamin A Deficiency, *J A M A* **102** 892 (March 24) 1934

(Footnotes continued on next page)

However, the reliability of earlier tests of dark adaptation has been questioned by many workers, and clinical results with various instruments have not shown sufficient correlation to warrant universal acceptance of the method. This is due mainly to the fact that certain instruments are not properly designed for positive detection of vitamin A deficiency. Others, though well suited to the purpose, are difficult to operate without some technical training. In the hands of inexperienced workers widely varying and hence inaccurate results are obtained. The sensitivity of different instruments also varies markedly, so that early deficiency states are not always perceived, and the patients are frequently classified as normal.

McCollum and his associates¹⁰ concluded: "At present there seems to be widespread skepticism as to the reliability of the dark adaptation technic as a measure of vitamin A deficiency." There is little doubt, however, that the difficulty lies in the technic of the earlier tests, the fundamental principle seems well established that both the speed and the ultimate extent of dark adaptation bear a direct relation to the vitamin A supply of the body.

The regenometer was designed as a diagnostic instrument that would be sensitive and accurate in the detection of subclinical vitamin A deficiency and at the same time be simple to operate and require a minimum of time per test. Its action is first to break down the visual purple of the retinal rods by a bright light and then to measure the speed with which this rod pigment is regenerated. In this the regenometer differs somewhat from most other instruments used in detecting night blindness. It measures the length of time required for the subject to perceive light of a fixed intensity rather than the intensity that can be perceived at a given moment.

Our experimental object in studies with the regenometer was two-fold: (1) to prove that by its use a subclinical vitamin A deficiency could be at least qualitatively detected, and (2) to determine its sensitivity in following the course of experimentally induced deficiency of vitamin A in normal subjects and the effect of vitamin A supplementation on this deficiency.

7 Jeans, P. C., Blanchard, E., and Zentmire, Z. Dark Adaptation and Vitamin A. A New Photometric Technic, *J. A. M. A.* **108** 451 (Feb 6) 1937.

8 Edmund, C., and Clemmesen, S. On Deficiency of A Vitamin and Visual Dvsadaptation, London, Oxford University Press, 1936, vol. 1, 1937, vol. 2.

9 Hecht, S., and Mandelbaum, J. The Relation Between Vitamin A and Dark Adaptation, *J. A. M. A.* **112** 1911 (May 13) 1939.

10 McCollum, E. V., Orent-Keiles, E., and Day, H. G. The Newer Knowledge of Nutrition, ed. 5, New York, The Macmillan Company, 1939, p. 313.

EXPERIMENTAL DATA

Method—The test is carried out in the following manner. The subject is first dark adapted for ten minutes, remaining in total darkness to compensate for previous conditions of light. A light-proof mask over the eyes is convenient for this purpose and enables one to avoid the difficulty of completely darkening a room. By its use, moreover, one subject can be dark adapted while another is being tested.

At the end of the preliminary dark adaptation the subject is seated at the instrument. Before him, 38 cm from his eyes, is a panel of translucent glass illuminated from behind, which serves as a source of light of constant intensity for breaking down the retinal pigment. He is asked to focus his eyes on a dark spot on the light panel during three minutes of light adaptation. As the vision is fixed on this spot, the image of the light panel covers a large field in the central part of the retina.

After three minutes the preadaptation light is turned off and two electric clocks, visible only to the operator, are automatically started. In the darkness the subject can see only a pinpoint of light on the panel. Actually, however, below this pinpoint and too dim to be visible at first, the test light is flashing on and off. The subject looks at the pinpoint until he can perceive the test light as it flashes. He then presses a push-button held in his hand, which stops one electric clock. The elapsed time recorded by this clock indicates how rapidly the visual purple has formed after exposure to the preadaptation light.

A second and confirmatory test follows the first. When the subject presses the button, not only is the first recording clock stopped but the flashing test light is automatically dimmed to a second constant value. When his eyes are able to perceive this light of lower intensity, the subject again presses the button, thereby stopping the second electric clock. Thus the regenometer measures two adaptation times.

Hecht and Mandelbaum⁹ have set forth certain test conditions that must be known in any valid studies of dark adaptation. The specifications for these conditions in regenometer tests are

1 The intensity of the "preadaptation" light is 31.2 millilamberts. Its image occupies a retinal field about 44 degrees in diameter.

2 The duration of the preadaptation light is three minutes, a period that was found advisable for this intensity.

3 The test spot is 1.9 cm in diameter, large enough to be easily perceptible even by persons with impaired visual acuity. Its retinal image is 2 degrees and 52 minutes in diameter. The two intensities of the test spot are 0.011 and 0.0044 microlamberts, respectively.

4 As the vision is centered on the pinpoint of light on the panel, the retinal image of the test light falls approximately 10 degrees above the fovea centralis. This part of the retina contains a high proportion of rods to cones and is accordingly more sensitive to dim light than are locations nearer the fovea.

5 The color of the test light is controlled by a violet filter which transmits only light of wavelength shorter than 475 millimicrons. The retinal rods, the adaptation of which it was considered desirable to test, are much more sensitive to violet light at these low intensities than are the cones. The rods cannot distinguish color, however, so that the test light appears gray to the subject. The test light is blotted out when the subject looks directly at it, as thereby its image falls over the fovea where there are only cones.

6 The test light flashes on intermittently for approximately one-half second, followed by approximately one-half second of darkness

Procedure—Ten healthy male students ranging in age from 19 to 24 years were selected from volunteers in various departments of Loyola University at Los Angeles. All were examined by an ophthalmologist for evidence of any visual pathologic condition that might influence the testing.¹¹

During experimental periods of forty-two to forty-five days the subjects ingested a diet low in vitamin A. Three alternate menus with estimated vitamin A contents ranging from 300 to 550 U S P units were given, with substitutes allowed for greater palatability. A supplement of vitamin B complex was added to this diet. Dark adaptation tests were made daily except on Sundays and holidays, usually at the same time of day for each subject.

Effect of Diet Low in Vitamin A on Dark Adaptation of Ten College Students

Subject	Age, Years	Height, Cm	Weight, Kg	Time Required to See Second Test Light, Min		Impaired Dark Adaptation† Appeared After	Return to Normal Range Followed Adminis- tration of Vitamin A After
				First Eight Days	On Diet Low in Vitamin A*		
D A	20	183 0	61 7	2 3	24½	10 days	Over 18 days
J R	24	170 0	61 2	1½ 2½	23½	17 days	Over 14 days
W B	19	180 4	64 8	1 2	6	29 days	10 days
M D	19	183 0	70 3	1½ 2	5	25 days	2 days
F M	20	167 5	73 8	1 2	4½	35 days	§
G S	20	180 4	79 3	1 1½	4	32 days	2 days
T H	20	178 0	80 3	1½ 2½	11½	25 days	7 days
J H R	20	170 0	81 6	1 1½	11½	22 days	Over 12 days
P G	21	173 0	83 4	1½ 2½	8½	30 days	6 days
J K	23	170 0	88 0	1 2	12	31 days	4 days

* Before administration of supplemental vitamin A

† Over three minute normal range

§ Given only 500 U S P units of vitamin A supplement daily, showed increased adaptation time of three to six minutes at the end of the experiment on his regular diet

OBSERVATIONS

As they continued on the diet low in vitamin A, all 10 subjects ultimately showed an increase in the time required to see the test lights. From original values of from one to three minutes, the time required to see the second test light increased to from four to twenty-four minutes with various subjects. This variation may have been due to the fact that some subjects consumed greater quantities of the diet or that utilization of the dietary vitamin A was more efficient in some subjects.

The increase was at first gradual, which suggested a steady depletion of vitamin A reserves. As depletion progressed, the increase became more pronounced. Some of the subjects did not become greatly depleted in the time available for the experiment.

¹¹ Ophthalmologic examinations were made by Dr Alfred R Robbins

There appeared to be a tendency for the tall, thin subjects to show impaired dark adaptation much earlier than did the shorter, heavier ones. While no definite conclusion can be drawn from these data, it would appear that subjects weighing over 73 Kg did not show adaptation time consistently out of the normal three minute range until the twenty-second to the thirty-fifth days (average, twenty-nine and two-tenths days). Those weighing less than 73 Kg tested out of the normal three minute range sooner—from the tenth to the twenty-ninth day (average, twenty and two-tenths days).

Unfamiliarity with the test procedure accounted for a few variable adaptation readings at the beginning. That these do not influence the essential results of the test is indicated by the fact that in only 1 instance in the first 80 tests did the time exceed the normal three minute range.

Even in persons whose adaptation time increased tenfold, no other symptoms directly traceable to nutritional deficiencies were observed during the experimental period. All subjects remained in good health and pursued their normal occupations as students. One subject reported a slight itching around the eyes when he was most night blind, and others reported that ocular fatigue was occasionally experienced after the low vitamin A diet had been followed for four or five weeks. However, this period coincided with intensive visual work in studying for examinations and preparing papers at the close of the school term. It is noteworthy that marked dysadaptation was detected long before the appearance of these uncertain symptoms.

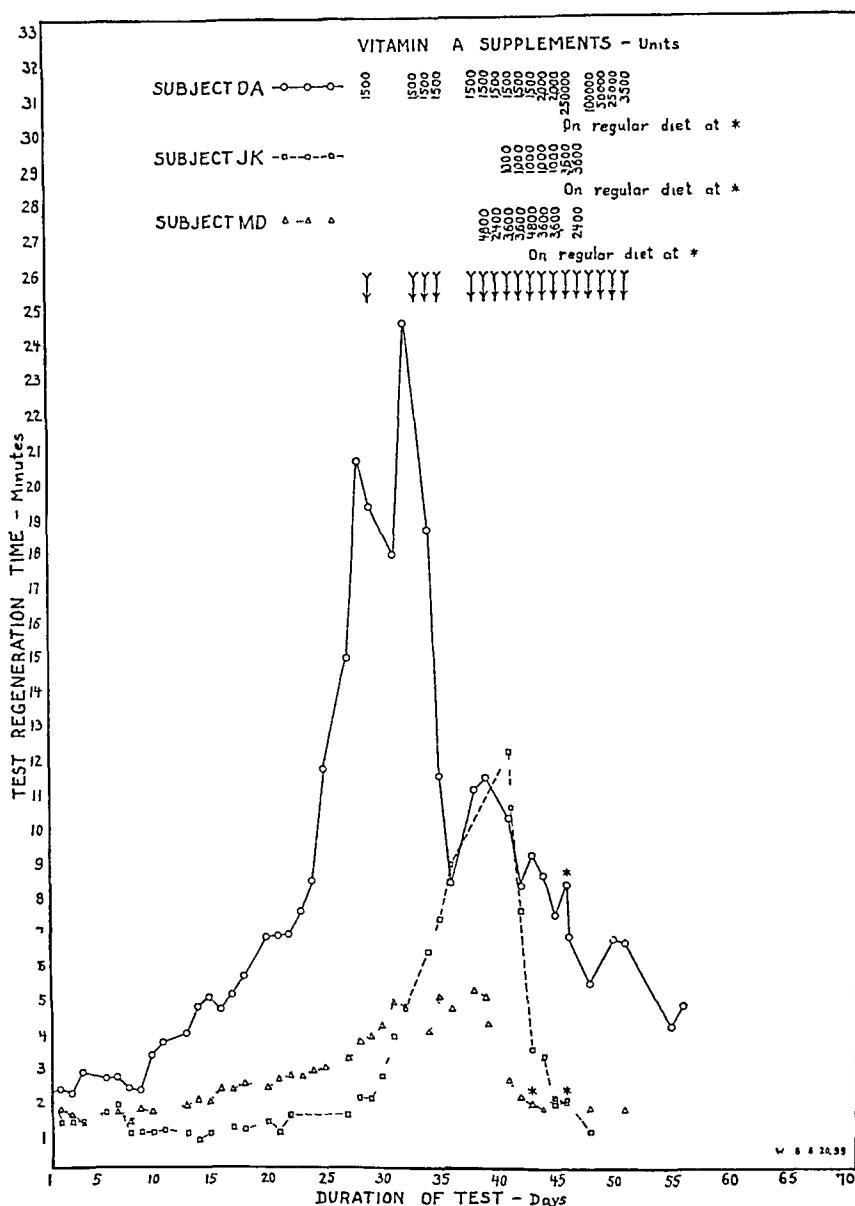
RELATION OF EXPERIMENTAL DYSADAPTATION TO VITAMIN A SUPPLY

All subjects were given vitamin A, some earlier than others because of faster depletion. Tests made the day after the first administration of vitamin A showed a decreased adaptation time except in 1 instance. In this case the subject received only 500 U S P units of supplementary vitamin A. In every case in which a test was repeated within one to three hours after the supplement was given, improved dark adaptation was observed.

The accompanying graph shows in detail the results with 3 subjects, D, A, J, K and M, D. These 3 were selected from the lowest, the middle and the highest sections of the group. The adaptation time as shown by the second test light has been given, because this measurement is believed to be of greater diagnostic value for latent vitamin A deficiency states than is measurement with the first test light.

Subject D, A was the first in the group to show impaired dark adaptation. The impairment appeared on the tenth day. His adaptation time increased from a normal value of two or three minutes to nineteen minutes on the twenty-ninth day on the low vitamin A dietary regimen. A single supplement of 1,500 U S P

units of vitamin A reduced the adaptation time, but on the third day following it had increased to twenty-four minutes. When D A was given a supplement of 1,500 U S P units of vitamin A for three consecutive days, U S P reference cod liver oil being used as a source, the adaptation time was immediately reduced to eight minutes, as is shown in the chart. Discontinuance of the supplement



Effect of a diet low in vitamin A on the dark adaptation time of 3 college students. Vitamin A supplementation is indicated by arrows.

for two days brought about an increase to eleven minutes. Thereafter the daily administration of 1,500 U S P units brought the period back to eight and one-half minutes. This was still above his normal adaptation value. Two thousand U S P units of vitamin A for two days brought about slight improvement.

The effect of massive doses of vitamin A was observed by feeding 25,000 to 250,000 U S P units in the form of cod liver oil concentrate. These doses failed

to decrease the adaptation time to a greater degree than did the much smaller doses previously used. Thereafter his normal diet was followed for four days, and his adaptation time was reduced to four to five minutes. Unfortunately, the experiment had to be terminated before his normal values could be regained.

Subject J K showed impaired dark adaptation on the thirty-first day. By the forty-first day the adaptation time had reached twelve minutes. He was given 1,000 U S P units of vitamin A as U S P reference oil, and his adaptation time decreased somewhat within a few hours. After four daily doses of 1,000 U S P units of vitamin A, his adaptation time decreased from twelve to two minutes. This amounts to about 17 units per kilogram of body weight (1,000 units in the supplement and 500 units in the diet). After two days of his regular diet plus 3,600 U S P units of vitamin A the time further decreased to one minute.

M D, as is shown in the chart, showed an increase in adaptation time above the normal on the twenty-fifth day. At thirty-nine days his adaptation time was five minutes. He was given a daily supplement of 3,600 U S P units of vitamin A, and within four days his adaptation time decreased to two minutes. With this supplement and his normal diet he remained at this level for eight successive days.

T H first showed impaired dark adaptation after twenty-five days on the low vitamin A dietary regimen. On the forty-first day his adaptation time was eleven and one-half minutes. After he had received 500 U S P units of vitamin A supplement daily for three days, the time decreased to five and one-half minutes. When he returned to his regular dietary regimen, plus about 2,400 U S P units of vitamin A daily, it took four additional days for his adaptation time to return to its normal value.

J H R had an adaptation time of eleven minutes after receiving the low vitamin A diet for thirty-nine days. He received 3,600 U S P units of vitamin A daily. After four days, during which his adaptation time decreased from eleven to eight minutes, he returned to his regular dietary regimen but continued the supplement. His adaptation had not returned to its normal value after eight more days.

P G received 500 U S P units of vitamin A daily after his adaptation time had reached eight minutes. After three days the time decreased to four and one-half minutes. A massive dose of 125,000 U S P units of vitamin A improved his testing time only thirty-eight seconds at four hours after administration. His values were normal after six days of supplementation.

W B received 500 U S P units of vitamin A supplement daily when (on the forty-first day of his low vitamin A diet) his adaptation time had increased to five and one-half minutes. This was sufficient to cause a temporary decrease in the adaptation time but not sufficient to maintain it. Five days of regular dietary regimen and supplementation with vitamin A brought him within the normal three minute range.

These data indicate the following conclusions: 1 The rate of depletion of stored vitamin A is variable. 2 Depletion, once initiated, proceeds relatively fast. 3 On the basis of these results an adaptation time of one to three minutes for the second test point may be considered normal. It was observed that normal subjects perceive the second test light within one minute of the first, but as depletion proceeds a pronounced spread occurs between the two adaptation states. These results offer confirmatory evidence of the deficiency state. 4 After administration of vitamin A there is at first a rapid utilization by the retina, as indicated by a rapid decrease in the adaptation time. However, continued administration of a vitamin A supplement produced improvement at a less rapid rate.

COMPARISON OF REGENOMETER WITH BIOPHOTOMETER

Dark adaptation tests were made on all subjects with the biophotometer at the time when most of the subjects showed the greatest adaptation times with the regenometer

The biophotometer readings for J R were well within the normal range when the regenometer gave an adaptation time of sixteen minutes, more than five times greater than normal P G gave a low biophotometer reading when his testing time of six minutes indicated only a mild deficiency by the regenometer

Most of the subjects were found to be within the normal range by the biophotometer This would seem to suggest a greater sensitivity of the regenometer in the detection of early states of vitamin A deficiency

COMMENT

The average depletion time for 6 subjects weighing over 73 Kg was twenty-nine and two-tenths days The average depletion time for 4 subjects weighing under 73 Kg was much less (twenty and two-tenths days) Whether a lower store of vitamin A, higher daily requirements or poorer utilization of carotene in the diet was responsible for more rapid depletion of the subjects of lower weight cannot be known from these data

In harmony with the observations of Booher, Callison and Hewston,¹² it is evident that in the return to the normal state there is at first a rapid, though suboptimal, mobilization of vitamin A in the retina Then follows a slower improvement, seemingly uninfluenced by a greatly increased vitamin A intake A supplement of only 500 U S P units of vitamin A per day produced rapidly improved dark adaptation in 2 subjects

For subject D A, a daily intake of approximately 2,000 U S P units of vitamin A (1,500 units in the supplement and 500 units in the diet) served to produce improved dark adaptation This is an intake of approximately 32 units per kilogram of body weight for this subject and hence falls well within the range of requirements suggested by Booher and her collaborators¹² This intake was fairly close to the twenty-four hour requirement, owing to the fact that suspension of the supplement for three days (thirtieth to thirty-second inclusive) caused a pronounced increase in the dark adaptation time The same observation was made when the supplement was suspended on the thirty-sixth to the thirty-seventh day The fact that this subject remained in the

¹² Booher, L E, Callison, E C, and Hewston, E M An Experimental Determination of the Minimum Vitamin A Requirements of Normal Adults, *J Nutrition* **17** 317, 1939

normal range for only the first ten days of the experiment indicates a previous suboptimal vitamin A intake, a low storage or an increased requirement

The feeding of massive doses of vitamin A, up to 250,000 U S P units, was not proportionately more effective than much smaller amounts (1,500 to 3,600 U S P units per day) in improving experimental night blindness caused by vitamin A deficiency

No clinical symptoms of vitamin A deficiency were observed during the course of the experiments

Relatively smooth curves even with the large number of experimental determinations indicate that the experimental errors were small

Unfortunately these studies were carried out late in the college year, and the subjects could not be retained for study as long as was desirable. A longer time than was available and a greater intake of vitamin A were evidently required for a complete return of 4 subjects to normal dark adaptation

SUMMARY

A simple and sensitive test for detecting impaired dark adaptation is described. The course of vitamin A depletion of 10 college students on diets low in vitamin A was followed with this technic. All the subjects required a longer time to see a test light of constant intensity as depletion progressed and showed improvement as vitamin A supplements were administered. Individual variations in dark dysadaptation were observed and are discussed.

PROTAMINE ZINC INSULIN A CLINICAL STUDY

REPORT OF A GROUP OF DIABETIC PATIENTS IN WHOSE CASES
GLYCOSURIA WAS DISREGARDED FOR ONE YEAR

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AND

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The purpose of this communication is to present our observations on a group of diabetic patients who have been observed for a year or more during treatment with one daily dose of protamine zinc insulin. Furthermore, we plan to discuss briefly our routine therapy as well as to review the events which contributed to the adoption of the principles presented in this publication.

Protamine zinc insulin has been used in the treatment of diabetes mellitus for nearly four years. True, the original compound as prepared by Hagedorn¹ has undergone slight modifications, but basically the product is still regular insulin which has been mixed with protamine (a simple protein) with small quantities of zinc added to the compound. The resulting mixture, a milky suspension, is much less soluble, and is therefore more slowly absorbed in the subcutaneous tissues, than the clear soluble insulin hydrochloride discovered by Banting and Best².

Since protamine zinc insulin became commercially available, in 1937, thousands of patients with diabetes mellitus have been treated with it, and certain definite clinical facts have been established by numerous clinicians in the United States and abroad. All have agreed that protamine zinc insulin acts more slowly than regular insulin, that during the first three to six hours it shows little, if any, activity as judged by its effect on the blood sugar, that its pharmacologic effect continues for at least twenty-four hours with moderate doses and longer with larger ones, that reactions, though less frequent, are characterized by suddenness of onset and are severe and prolonged and that patients have reported a definite subjective improvement.

From the New York Hospital and the Department of Medicine, Cornell University Medical College

1 Hagedorn, H. C., Norman Jensen, B., Krarup, N. B., and Wodstrup, I. Protamine Insulinate, J. A. M. A. **106** 177 (Jan 18) 1936

2 Banting, F. G., and Best, C. H. J. Lab. & Clin. Med. **7** 251, 1922

We were particularly attracted to protamine zinc insulin because of the possibility of using a single dose of the preparation instead of the customary two, three or even four daily injections necessary with regular insulin. However, the use of a single dose of protamine zinc insulin proved disappointing with our patients with moderately severe and severe diabetes mellitus. With the diets employed at our clinic (200 to 250 Gm of carbohydrate) our patients revealed either intermittent or continuous heavy glycosuria. When we attempted to treat the glycosuria by increasing the dose of protamine zinc insulin, the urine became free from sugar but the patient suffered from insulin reactions, at times of alarming severity. To obtain the "physiologic" or "ideal" regulation, that is, maintenance of the urine free from sugar, we attempted various dietary divisions and also withheld the easily absorbable carbohydrates as suggested by Pollack,³ but our efforts were fruitless. All of these observations were on ambulatory patients of the clinic. On numerous occasions we observed that some of the patients, though they received one dose of protamine zinc insulin a day and revealed marked glycosuria, enjoyed good health, were in fine spirits, maintained their weight and were remarkably free from any symptoms of diabetes mellitus. We could not help being profoundly impressed and influenced by these observations, and it occurred to us that perhaps the criteria for satisfactory treatment of diabetes would have to be reevaluated. Was it possible that with protamine zinc insulin such fundamental therapeutic criteria as urine free from sugar and a normal value for blood sugar might stand revision? Was it at all likely that the patient's actual condition, that is, his weight, his ability to "carry on," his well-being and his psychic outlook, might be a more important guide than the height of the concentration of blood sugar and the glycosuria? How safe was it to allow our patients to excrete large quantities of dextrose over long periods? Would they have ketosis on this regimen of one single dose of insulin with continuous glycosuria? The question of the effect of continuous hyperglycemia and glycosuria on the frequency and severity of infections was also a consideration. With constant teaching by physicians of great experience in the field of diabetes mellitus that a normal level of blood sugar and urine free from sugar were the absolute essentials for satisfactory therapy, it was extremely difficult for us to reconcile this orthodox view with our clinical observations, namely, that a patient could feel perfectly well and be free from symptoms while revealing so-called poor control as evidenced by hyperglycemia and glycosuria. It was our feeling that an answer to our question would be more satisfactorily obtained with hospitalized patients,

3 Pollack, H. J. Mt. Sinai Hosp. 4: 437, 1938.

whom we could observe with great care and detail. We, therefore, admitted 2 patients with severe diabetes to the metabolism ward for study. The results of this work have been published in detail elsewhere.⁴ Briefly, our observations were that these patients, who received one dose of protamine zinc insulin daily as well as a diet of 1,640 calories composed of 75 Gm of protein, 60 Gm of fat and 200 Gm of carbohydrate, could maintain their weight, be in nitrogen equilibrium, excrete no ketone bodies in the urine and be absolutely free from symptoms even though they excreted an average of 100 Gm of dextrose a day over one experimental thirty day period and presented consistently high values for blood sugar. These patients were observed for fifty and sixty days each, and from the data obtained we postulated as a working hypothesis the following criteria for satisfactory treatment of diabetes mellitus with protamine zinc insulin:

- 1 Maintenance of weight
- 2 Absence of ketone bodies in the urine
- 3 Freedom from the following symptoms
 - a Thirst
 - b Polyuria
 - c Frequency of urination
 - d Hunger
 - e Weakness, fatigue
 - f Polyphagia
 - g Pruritus (limited to the genitalia, chiefly in females)
 - h Visual disturbances

In arriving at these conclusions we felt that it was the *utilization* and not the excretion of carbohydrates which was of prime importance, and that with patients treated as described the glycosuria was not an undesirable feature, as it protected the patient from reactions. This view has been substantiated in principle by recent publications,⁵ the major difference being a quantitative one. Even the most conservative observers feel that with the use of protamine zinc insulin glycosuria is compatible with good therapy. Some permit excretion of only 10 per cent of the carbohydrate intake, others, as much as 20 per cent.

Employing the single dose method and using the criteria outlined as guides for satisfactory treatment, we have treated 84 patients. All

4 Tolstoi, E, and Weber, F C, Jr. Protamine Zinc Insulin Metabolic Study, Treatment in Two Cases of Severe Diabetes by Equally and Unequally Divided Diets, with Comments on Criteria for Treatment, Arch Int Med **64** 91 (July) 1939

5 Joslin, E P. Mil Surgeon **82** 1, 1938. White, P. South M J **31** 15, 1938. Protamine Insulin and Diet in Diabetes Mellitus, editorial, Ann Int Med **11** 2048, 1938.

the observations were carried out in the outpatient department, and consequently all of our patients were ambulatory

We did not even attempt to "desugarize" our patients. Of course, if the patient maintained his weight on the prescribed diet and with the single dose of protamine zinc insulin revealed no glycosuria, the therapy was continued. However, if the patient continued to excrete sugar and revealed no evidences of loss of weight or ketosis, no effort was made to obtain a specimen free from sugar by altering the diet or the dose of insulin or both. There were 27 patients in whose cases such observations were made. All of these revealed almost continuous glycosuria during a year or longer. The glycosuria was determined qualitatively only. The group was composed of the average type of clinic patient, whose health was absolutely essential for livelihood. The diet was never weighed. It was always calculated on the basis of household measures and at best was only an approximation. All of the patients were instructed to take a glass of milk and three crackers or a slice of bread at bedtime. They were requested to test their urine for purposes of record and were advised not to be upset if the analysis revealed sugar. They were cautioned, however, that if thirst, frequency of urination or unusual hunger appeared they should report to us at the clinic. Usually when the patient arrived his weight and pulse rate were recorded. A portion of a twenty-four hour specimen of urine from the preceding day was then examined by the nurse in charge, and the findings (chiefly for dextrose and acetone) were entered on the chart. The patient then consulted with the dietitian, and an approximate estimate was made of the food intake of the past twenty-four hours. During these consultations the patient was given an opportunity to ask all sorts of questions in connection with his diet. In other words, the consultations with the dietitian were not limited to analyses of the intake but were of educational value. After all these preliminaries the patient would see the physician, who noted the patient's weight and the results of the tests for acetone and then questioned the patient concerning symptoms. If our criteria for satisfactory treatment were fulfilled, that is, if there was no loss of weight, no symptoms and no ketonuria, no therapeutic changes were made even though 4 plus glycosuria was present. If, however, there were a loss of weight and glycosuria, the amount of protamine zinc insulin was increased at frequent intervals until there was a gain of weight. For example, if the patient had been receiving 35 units of protamine zinc insulin and with this dosage and a diet which we felt was calorically ample for him was revealing glycosuria and losing weight, the dose of insulin was increased to 45, 50 or even 60 units, until he ceased to lose weight or gained. As soon as we could demonstrate a gain or even maintenance of weight the glycosuria was disre-

garded. No determinations of the concentration of blood sugar were made systematically in these cases.

Very rarely because of a slight cold and also at times without any obvious cause a slight trace of acetone was found in the urine. This was never of serious consequence. It was treated by the administration of salt tablets, 1 Gm (two 0.5 Gm pellets) every two hours, with a glass of water for each dose. In addition, hot salty broths were recommended. Usually the acetone disappeared, but when it persisted or increased one or two small doses of regular insulin usually sufficed to render the urine free from acetone. Of the 84 patients observed, only 27 revealed glycosuria almost constantly present during the period of treatment, that is, a year or more. The remaining group showed only occasional glycosuria and revealed no clinical symptoms. Since this is acceptable by all as satisfactory control, no comment on this group is necessary. However, we wish to present in some detail the records of the 27 patients in whose urine sugar was almost constantly present for over twelve months.

An examination of the tabulated data shows that there were 10 male and 17 female patients, whose ages varied from 15 to 71 years. The diabetes was moderately severe and severe, and its duration was from one to fourteen years. The dose of insulin varied from 10 to 60 units, with an average of about 25. The carbohydrate fraction of the diet was 150 Gm lowest and 250 Gm highest. All of the patients revealed variable glycosuria, from zero to 4 plus with the latter a more frequent finding. Five of the patients showed 4 plus glycosuria⁶ at every examination. Nineteen of the 27 patients gained weight, the minimum gain was 0.2 Kg and the maximum 14.4 Kg. Six lost weight (maximum, 5.4 Kg, minimum, 0.2 Kg). Two patients neither gained nor lost. None of the patients presented any symptoms of diabetes even though glycosuria was present. There were no unusual infections. The common cold was seen in several of this group, but at no time was it incapacitating. Only 1 of this group revealed occasional acetonuria. This was observed whenever the patient had a cold. It was never severe and did not require any other treatment than the salt tablets, fluid and one or two additional doses of regular insulin.

We then reviewed the records of the patients who lost an appreciable amount of weight while under observation. We noted that their weight did not always continue to fall. There were oscillations throughout the year, and we have merely presented their weights at the beginning and end of the period of protamine zinc insulin therapy. Brief summaries of their records are given (for further data, see table).

6 As determined by red or yellow staining with Benedict's solution.

Data on Twenty-Seven Patients with Diabetes Mellitus Treated with Protamine Zinc Insulin

Case	Sex	Age	Duration of Diabetes		Duration of Treatment with Protamine Zinc Insulin		Number of Units	Approximate Diet, Gm			Glycosuria (Qualitative)	Weight		Change in Weight, Kg	Symptoms During Treatment
			Yrs	Mos	Yrs	Mos		Protein	Fat	Carbohydrate		Before Protamine Insulin	After Protamine Zinc Insulin		
1	F	17	2		1	10	25.60	70	60	225	4 plus continuously*	47.3	54.4	+ 7.1	None
2	M	15	2½		2	1	14.16	100	110	250	0 ½ plus	48.0	56.7	+ 8.7	None
3	F	56	2½		1	2	23.20	75	50	170	2 ½ plus	57.1	59.9	+ 2.8	Frequent colds last winter
4	F	61	7		1	3	33.45	70	70	175	1 ½ plus	58.7	56.6	- 2.1	Tooth extracted no difficulty
5	F	58	7		1	4	40	80	70	200	0 ½ plus	46.3	47.9	+ 1.6	None
6	F	19	7		3		50	75	80	130	4 plus continuously	48.2	51.0	+ 2.8	None
7	M	51	1	4	1	4	30.20	70	60	150	0 2 plus	66.0	70.0	+ 4.0	None
8	M	17	3	10	3	10	15.20	80	90	220	4 plus continuously	44.5	53.6	+ 9.1	None
9	F	53	2	10	1	3	25	60	90	195	0 2 plus rare ½ plus	53.7	58.5	+ 4.8	None
10	F	48	10		1	5	40.45	60	60	225	2 ½ plus	51.2	56.0	+ 4.8	None
11	F	19	11		1	6	30.40	70	50	140	1 ½ plus	55.8	56.4	- 2.4	Occasional headaches for 6 years
12	M	41	4½		1	6	20.30	70	70	200	4 plus continuously	61.1	61.0	± 0	Toothache and extrusion, no complications
13	M	30	2		1	7	20.29	90	120	250	0 3 plus	63.8	64.6	+ 0.8	Occasional reactions
14	F	47	9		1		23.30	65	70	200	½ plus continuously	63.0	62.8	- 0.2	None
15	F	23	5		1	8	50	75	115	125	½ plus	60.0	58.0	- 2.0	None
16	F	68	7		1	1	23.20	80	65	200	0 2 plus	61.1	75.5	+14.4	None
17	M	32	3	10	1	4	23.20	70	60	200	1 ½ plus	60.4	60.0	- 0.4	None
18	M	61	2½		2		10	90	60	250	0 4 plus	71.7	69.3	- 5.4	None
19	M	28	1	4	1	1	30.40	90	90	250	0 ½ plus	60.1	64.4	+ 4.3	None
20	F	30	2	10	1	7	30	70	70	150	0 4 plus	46.3	52.0	+ 5.7	None
21	F	16	6		1	4	25	70	80	200	1 4 plus	48.2	50.0	+ 1.8	None
22	M	71	14		1		20.35	70	50	175	0 4 plus	68.7	69.9	+ 0.3	Pain on walking
23	F	64	4		1	1	15	70	50	175	0 3 plus	44.0	44.3	+ 0.3	None
24	F	61	4		1	4	20	70	60	150	0 2 plus	66.9	70.6	+ 3.7	None
25	M	35	2	10	1		20	100	80	250	0 3 plus	69.0	75.2	+ 6.2	None
26	F	16	1		1		40	70	65	250	4 plus continuously	48.2	51.5	+ 2.7	None
27	F	24	5		2		25.55	80	75	250	2 4 plus	70.0	70.0	+ 0	Occasional colds

* Occasional acetone

REPORT OF CASES

CASE 4 (loss of 21 Kg) —J C had severe diabetes. When a single daily dose of 35 units of protamine zinc insulin was started, in June 1938, she weighed 58.7 Kg. Six months later she weighed 56.9 Kg. At this point the diet was increased, and her weight two months later rose to 58.5 Kg. Later, during the summer months, she lost 1 Kg. because of the heat and a poor appetite. She had some dental extractions during this period, with excellent healing. Her present weight is 56.6 Kg.

CASE 11 (loss of 24 Kg) —F B had been taking 30 units of protamine zinc insulin daily, and on admission to the clinic, November 1938, she weighed 58.8 Kg. She has schooled herself in eating less than is prescribed, but at one period (May 1939) when she did enjoy her full diet her weight rose to 60 Kg.

CASE 15 (loss of 2 Kg) —F H has been studied in detail in the metabolic service, and her loss of weight was noted while she was in the hospital on a sub-caloric diet of 1,650 calories. On admission to the hospital she weighed 60 Kg. On discharge her weight was 58 Kg. Seven months later her weight was 59 Kg.

CASE 18 (loss of 54 Kg) —A mildly diabetic patient has been receiving 10 units of protamine zinc insulin. His diet and insulin dosage have been very irregular, the latter having been omitted occasionally for seven to ten day periods.

COMMENT

From the study of this group of 84 diabetic patients in the outpatient department who for one year have received one daily injection of insulin and in whose cases no particular effort was made to maintain the urine free from sugar, it is seen that only 27 revealed persistent glycosuria throughout the period of observation. These 27 patients were in good health, and furthermore they were in a state of social and economic usefulness. Not only did the majority of them maintain their weight, but some gained weight, even though heavy glycosuria was almost continuously present. There were no complaints or symptoms at any time associated with the glycosuria, and infections were no more frequent in this group than in the group whose urine was mostly free from sugar. All the patients in this group enjoyed much more freedom, as there appeared no necessity for careful dietary measurements, and it was not necessary for them to carry with them their syringe and insulin. They administered the insulin to themselves in the morning and then put the equipment away until the following day. Thus, the patients were not singled out as a group apart from their fellow men, and their habits of living approximated the normal ones.

At this point it may be argued that since we direct our efforts toward making the lives of this group normal as to living habits, why not extend our efforts in the direction of "physiologic normality" so far as the diabetes is concerned, that is, toward obtaining urine free of sugar and possibly a normal level of blood sugar, as these objectives

have been considered synonymous with proper utilization of the carbohydrates? This may be sound, but what evidence is there to show that with protamine zinc insulin such utilization of carbohydrates does not take place in spite of hyperglycemia and glycosuria? None whatever. Glycosuria has been such a dominant component in the study of the treatment of diabetes that the more important factor of utilization has been almost totally ignored, although it was emphasized long ago by the Russell Sage group of investigators.⁷

In 1914, Allen and DuBois^{7b} presented calorimetric studies on diabetic patients showing that the diabetic person can and does utilize carbohydrate in the presence of hyperglycemia and glycosuria. Some of their patients showed a maximum utilization of carbohydrate, as judged by the respiratory quotient, when the carbohydrate fraction of the diet was at its maximum and the glycosuria at its highest level. For a short period, while these patients were observed with the calorimeter, they revealed a capacity to utilize carbohydrate approaching the physiologic ideal. Additional evidence that such utilization of carbohydrate takes place even in the presence of the most severe diabetes has been published by Gephart, Aub, DuBois and Lusk.^{7a} The experimental subject, Cyril K., with very severe diabetes, was able to derive 62 per cent of his total calories from carbohydrate when given a diet of 60 Gm of protein, 60 Gm of fat and 252 Gm of carbohydrate, a most unorthodox diet for that era but evidently effective in promoting the utilization of carbohydrate. The authors stated "This astonishing result shows that Cyril K., who two months before had been completely diabetic, was now able to derive two thirds of his basal requirement for energy from the oxidation of carbohydrate." This group of observers established with certainty that for short periods, at least, the diabetic patient, irrespective of the severity of the disorder, is capable of utilizing carbohydrate. Unfortunately the process did not continue. Today one can prolong this utilization of carbohydrates by means of insulin, so that in place of the short duration of the so-called physiologic ideal, utilization, a longer duration is produced. If this postulate is accepted, hyperglycemia and glycosuria must be of secondary importance. The most important and physiologic basis for satisfactory treatment, therefore, is *not how much sugar is excreted but how much is metabolized*. Recently, Bridge and Winter⁸ have studied this question of carbohydrate metabolism while noting the effect of insulin on diabetic patients. They found no correlation whatever between the height of the

7 (a) Gephart, F. C., Aub, J. C., DuBois, E. F., and Lusk, G. Metabolism in Three Unusual Cases of Diabetes, Arch Int Med **19** 908 (May) 1917. (b) Allen, F. M., and DuBois, E. F. Metabolism and Treatment in Diabetes, *ibid* **17** 1010 (June) 1916.

8 Bridge, E. M., and Winter, E. A. Bull Johns Hopkins Hosp **44** 257, 1939.

value for blood sugar and the respiratory quotient in cases of diabetes treated with insulin. They reported also that with wide fluctuations from the hyperglycemic to the hypoglycemic level there was no indication that carbohydrate was being utilized at different rates. In other words, these investigators have clearly demonstrated that in an insulin-treated diabetic person carbohydrate is utilized in the presence of hyperglycemia and sequential glycosuria. They concluded that in view of these important findings neither the value for blood sugar nor the degree of glycosuria is an adequate criterion for the regulation of diabetes. Their conclusion is particularly applicable to patients treated with protamine zinc insulin, in whom carbohydrate utilization can be maintained as long as the insulin is active.

From the clinical side we have gathered evidence which has led us to similar conclusions. We feel that if a state of carbohydrate utilization can be maintained in the diabetic person (and this is readily accomplished by the use of protamine zinc insulin) a physiologic state has been created, and furthermore it is our feeling that the guiding principles for such a status in the presence of glycosuria and hyperglycemia are (1) maintenance of weight, (2) freedom from symptoms of diabetes and (3) absence of ketone bodies in the urine.

SUMMARY AND CONCLUSIONS

Eighty-four patients with diabetes mellitus were treated with one daily dose of protamine zinc insulin. No particular effort was made to maintain the urine free from sugar, and yet only 27 patients revealed almost continuous glycosuria throughout the period of study (one year). The results in this group are presented in detail. Briefly, the great majority of them maintained their weight, and many gained. None presented any symptoms of diabetes mellitus, and only 1 revealed mild acetonuria (on very rare occasions). Their diets were not weighed. The incidence of infections was no greater in this group than in other patients. Guiding principles for the treatment of diabetes mellitus with protamine zinc insulin are proposed. These are based on clinical and experimental studies. The facts are presented and the theoretic concepts discussed.

EVALUATION OF VITAMIN B THERAPY FOR DIABETES

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Several investigators have published results indicating a definite value of vitamin therapy for diabetes¹. Careful survey of their publications, however, reveals lack of a proper period of control of diabetes before institution of the therapeutic tests. In few of the case histories described are there evidences of stability in the diabetic state before the special therapy was initiated. Thus it is always doubtful whether the improvement observed was due to the vitamins given or to the continued regulation of dietary and insulin needs. Diabetic patients were often given vitamin preparations while they were still improving under previously instituted dietary and insulin regimens, and any further improvement was credited to the vitamin.

Good results have been claimed for administration of thiamine and ascorbic acid to diabetic persons, even though most diabetic diets are adequate in these two substances. Since these claims seem to have been based in most instances on improperly controlled patients, we have undertaken a similar study on patients well standardized for six to eighteen months prior to the period of administration of vitamins. Under such conditions of adequate control of the patient thiamine and riboflavin are found to produce no noticeable alteration in the diabetic state, except for an amelioration of neuritic pain by thiamine.

1 Vorhaus, M G, Williams, R R, and Waterman, R E. Studies on Crystalline Vitamin B₁. Observations in Diabetes, *Am J Digest Dis & Nutrition* **2** 541-554, 1935. Dienst, C. Ist der Diabetes durch die Vitamine B und C beeinflussbar? *Deutsche med Wchnschr* **65** 710-715, 1939. Pfleger, R, and Scholl, F. Diabetes und Vitamin C, *Wien Arch f inn Med* **31** 219-230, 1937.

METHODS

A group of 25 outpatients from the diabetic clinic of the Cincinnati General Hospital were selected as clinical test material for study. All were considered to have moderate to severe diabetes. Their ages varied from 18 to 66 years. All had been adequately controlled for many months before this period of study began, except 2 patients with neuritis, whose control treatment began with, or shortly before, this study. In no case did serious infection complicate the study. Except for an increase in the 2 cases of neuritis, the dietary values were held constant throughout the period of study at the same level that had prevailed for months previously. Changes in the insulin dosage were few and are recorded in table 1. The weight of each patient was recorded at the beginning of the study and watched

TABLE 1—*Thiamine Moderate Doses*

Patient	No	Age	Sex	Weight, Pounds		Diet	Insulin, Units		Thiamine		Symptoms Present		Symptoms Improved	
				Before	After		Beginning	End	Daily Dose, Mg	Weeks Given	Specific	Nonspecific	Specific	Nonspecific
B A	1	56	M	144	143	See table 5	20	30	33	16	+	+	++	++
W C	2	24	M	126	127		35*	35*	33	16	0	0	0	0
F N	3	59	F	127	126		32*	32*	33	14	0	+	0	++
X C	4	52	M	151	140		50*	50*	33	16	0	0	0	0
I J	5	54	F	103	119		50*	40*	33	16	+	+	++++	++++
R B	6	57	M	115	119		50*	45*	23	8	0	+	0	+, -
I S	7	56	F	132	131		18*	15*	33	14	0	+	0	+
L B	8	53	M	158	154		30	30	33	16	0	+	0	++
C B	9	20	F	148	153		53*	56*	33	16	0	0	0	0
J N	10	31	M	125	126		45*	45*	33	16	0	+	0	0
J M	11	18	M	145	146		45*	45*	33	16	0	0	0	0
T R	12	54	F	168	170		50*	50*	33	16	0	0	0	0
J S	13	48	M	143	142		50	44	33	8	0	+	0	+, -
S P	14	66	F	124	122		15	15	33	16	0	+	0	0
G A	15	57	F	122	127		30*	30*	33	16	0	+	0	0
L B	16	37	F	122	123		52†	52†	33	14	0	+	0	++
R H	17	32	M	150	146		40†	40†	23	14	0	+	0	++
J D	18	20	M	121	125		50*	50*	33	12	0	0	0	0
N R	19	40	F	120	120		15*	30*	33	16	0	0	0	0
J M	20	46	M	156	153		30	30	33	16	0	+	0	0

* Protamine zinc insulin

† Crystalline zinc insulin

throughout the period. Control of the diabetic state in these patients was determined by examination of the usual four daily specimens of urine for sugar. During the entire period of study only 2 patients showed occasionally more than a 1 plus reaction for sugar in the urine, the others usually excreting no sugar or only a trace.

In order to leave no doubt that the patients received the full effect of all thiamine prescribed, thiamine chloride solution (10 mg per cubic centimeter) was added to the insulin used, and the patients were advised as to the proper correction in dosage volume to cover their insulin needs. No apparent reaction between the insulin and the thiamine occurred,² and the blood sugar-lowering effect of the insulin remained unaltered (as carefully tested on 3 patients). Riboflavin was administered orally, 2 mg daily.

² The manufacturer states "It is our opinion that neither the potency of insulin nor vitamin B₁ is appreciably affected when the two are together in solution."

RESULTS

Thiamine Therapy—The thiamine-insulin mixture was given to 20 well regulated diabetic patients in amounts sufficient to cover their insulin needs and to supply 33 mg of thiamine daily. After eight, twelve and sixteen weeks respectively of this regimen, the dose of thiamine was increased to 5 mg daily for 3 of these same patients, and to 83 mg for 1 other after eight weeks. Table 1 indicates the details of diet, the insulin and thiamine dosage and the therapeutic results obtained with these 20 patients during the period of thiamine therapy.

No effects of the thiamine were observed either in the general nutritional state of the patients or in their dietary or insulin needs for proper control of the diabetic state. One patient gained 16 pounds (7.3 Kg) in weight, another lost 11 pounds (5 Kg). The greatest reduction in the dose of insulin during the sixteen week period was a reduction of 10 units daily for 1 patient, who had been brought under control only shortly before beginning the thiamine therapy. An increase of 15 units for another patient was necessary to cover a dietary addition. A third patient, who was sometimes careless as to food intake, required an increase of 10 units during the period. All 20 patients were maintained at a control level, so that occasional traces of sugar appeared in the urine but insulin reactions were absent. It seems safe to say, therefore, that thiamine therapy within reasonable limits does not appreciably alter the diabetic state of previously well controlled patients.

An attempt to evaluate the effects of thiamine on the general symptoms of each patient is difficult. Except in 2 patients, no specific symptoms were present. Several patients had various complaints before and during the study, such as lack of appetite, ease of fatigue, lack of "pep" and indefinite pains here and there. Of the 11 patients with these indefinite complaints, 6 showed no change, and 5 reported rather definite improvement. The appetite of these 5 was better, they did not tire so easily and felt generally stronger. The thiamine solution was withheld from these 5 patients without their knowledge, and 3 of them continued to show the same improvement, while 2 noted a slight reduction in their feeling of improvement. Two of the group reported marked improvement after one week of the added thiamine therapy, however, in three more weeks the feeling of improvement had changed to the opposite. Both asked to have administration of thiamine discontinued. There were, however, 2 patients with definite diabetic neuritis. One of these was the newly controlled patient, and the other was the least cooperative subject. Both showed definite improvement of their neuritic symptoms, the former being completely relieved within about three months and the latter much improved.

Table 2 shows the results of large doses of thiamine. The patients had already received 33 mg of thiamine and had not improved. Doses of 5 mg were then given to 3 and a dose of 83 mg to the other. There was a loss of weight in 1, which was probably due to the fact that he reduced his own diet. The dose of insulin was reduced 5 units for

TABLE 2—*Thiamine Large Doses*

Patient	No	Age	Sex	Weight, Pounds		Diet	Insulin, Units		Thiamine		Symptoms Present		Symptoms Improved	
				Before	After		Beginning	End	Daily Dose, Mg	Weeks Given	Specific	Nonspecific	Specific	Nonspecific
J M	11	18	M	146	146	See table	45*	45*	5	8	0	0	0	0
J S	13	48	M	142	142	5	44	44	83	8	0	+	0	0
R B	6	57	M	119	107	5	45*	40*	5	8	0	+	0	0
J N	10	31	M	126	126		45*	45*	5	8	0	+	0	0

* Protamine zinc insulin

TABLE 3—*Riboflavin*

Patient	No	Age	Sex	Weight, Pounds		Diet	Insulin, Units		Riboflavin		Symptoms Present		Symptoms Improved		
				Before	After		Beginning	End	Daily Dose, Mg	Weeks Given	Specific	Nonspecific	Specific	Nonspecific	
I J	5	54	F	119	122	See table 5	20*	20*	2	8	0	0	0	0	
Z J	21	57	M	138	138		42*	40*	2	8	0	0	+	0	
R C	22	34	M	174	173		60†	60†	2	8	0	0	0	0	
A M	23	29	M	139	135		42*	42*	2	8	0	0	0	0	
G A	15	57	F	127	126		30*	30*	2	8	0	+	0	0	
W R	24	58	M	117	117		40	40	2	8	0	+	0	0	
J S	13	48	M	142	143		44	44	2	8	0	+	0	+	
R B	6	57	M	107	107		40*	40*	2	8	0	+	0	+	
C P	25	64	F	103	103		8*	8*	2	8	0	+	0	0	
F N	3	59	F	126	126		32*	32*	2	8	0	0	0	0	
B															
G A	15	57	F	126	124		30*	30*	2‡	8	0	+	0	0	

* Protamine zinc insulin

† Crystalline zinc insulin

‡ 33 mg of thiamine given with the 2 mg of riboflavin daily

the same patient, the reason for this being the reduction in diet. The others showed no change in weight, diet or insulin need, and none of the 4 reported any change in general feeling. It seems evident that even with large doses of thiamine chloride administered to well controlled diabetic patients the diabetes is not appreciably changed.

Riboflavin Therapy—In table 3 are shown the effects of riboflavin administered to 10 of the 25 diabetic patients. No appreciable change in weight occurred, the diets remained constant and all the patients continued to be satisfied. The insulin requirements remained the same,

except for a reduction of 5 units for 1 patient. There was some improvement in the general feeling of 2 patients. Riboflavin given in large amounts seems not to alter the degree of severity of diabetes. The patients afterward had no less severe diabetes than before the study began.

Thiamine-Riboflavin Therapy—One of these patients was given a thiamine-insulin mixture to provide 3.3 mg of thiamine and, in addition, 2 mg of riboflavin daily by mouth. At the end of eight weeks no changes were found in weight, diet, insulin requirement or general feeling. Apparently with large doses of thiamine and riboflavin administered together to a well controlled diabetic patient no change occurs in the severity of the diabetic condition.

TABLE 4—*Alfalfa Extract*

Patient	Age	Sex	Weight, Pounds		Diet, Gm			Insulin, Units		Alfalfa		Symptoms Present		Symptoms Improved	
			Before	After	Carbohy- drate	Protein	Fat	Beginning	End	Daily Dose, Ounces	Months Given	Specific	Nonspecific	Specific	Nonspecific
W M	29	M	148	147	135	90	120	50	50	3	4	0	+	0	0
J M	17	M	138	141	150	80	110	45*	45*	3	4	0	0	0	0
R M	16	F	112	130	150	80	80	70*	70*	3	4	0	0	0	0
Z J	55	M	142	138	160	80	100	42*	42*	3	4	0	+	0	+
M G	70	F	122	125	150	80	125	0	0	3	4	0	+	0	++
C D	61	M	118	122	200	80	135	20	20	3	4	0	+	0	++
W S	77	M	136	139	150	80	60	0	0	3	4	0	+	0	++
R B	57	M	113	115	170	80	120	40*	30*	3	4	0	+	0	0
J S	46	M	141	143	150	85	110	50*	50*	3	4	0	+	0	0
C B	19	F	148	148	180	100	70	45*	50*	3	4	0	0	0	0

* Protamine zinc insulin

Alfalfa Extract Therapy—A crude acid-alcoholic extract of powdered alfalfa leaves³ was given to 10 of the well standardized patients for four months, again without definite influence on the diabetic state (table 4). Alfalfa leaves afford a rich source for all vitamin B fractions but contain little vitamin C. The crude extract is used satisfactorily and in large amounts in our outpatient clinic as a general tonic and for patients suspected of suffering from vitamin B inadequacy. As is commonly found with nondiabetic patients of older age groups, the diabetic patients given the alfalfa extract reported improvement in gen-

3 The extracting menstruum contained 0.4 per cent hydrochloric acid and 15 per cent ethyl alcohol. After two weeks' extraction of the powdered leaf, sodium hydroxide was added until the reaction remained only faintly acid to litmus, the heavy protein precipitate was filtered out and the alcohol content was brought up to 25 per cent by volume for preservation.

eral well-being,⁴ but no change was found to occur in their diabetic state. So long as the dietary intake was kept constant, no alteration was found in their insulin requirements.

Thiamine and Riboflavin Content of Diabetic Diets—In order to obtain an estimate of the patients' dietary intake of thiamine and riboflavin, close check was kept on the food actually consumed by each patient. Only the most reliable and cooperative patients were chosen for the study, so we feel that their statements as to food consumed are

TABLE 5—*Thiamine and Riboflavin*

Patient	No	Diet				Thiamine, Micro grams	Riboflavin, Micro grams	Total Nonfat Calories, Ratio
		Carbohy- drate, Gm	Protein, Gm	Fat, Gm	Calories			
B A	1	140	70	80	1,560	730	1,266	0.87
W C	2	170	70	100	1,860	1,050	2,154	1.09
F N	3	120	64	80	1,460	940	1,185	1.27
X C	4	175	75	110	1,990	765	1,175	0.76
I J	5	200	70	80	1,800	827	1,223	0.77
R B	6	175	80	110	2,010	982	1,171	0.96
I S	7	100	65	90	1,470	740	1,075	1.12
L B	8	170	85	110	2,010	1,091	1,307	1.06
C B	9	80	60	50	1,010	680	1,173	1.21
J N	10	150	85	140	2,200	874	1,405	0.93
J M	11	150	80	110	1,910	815	1,594	0.89
T R	12	110	60	40	1,040	769	731	1.13
J S	13	150	75	110	1,890	813	1,617	0.90
S B	14	120	70	80	1,480	469	1,715	0.62
G A	15	140	85	135	2,115	832	850	0.92
L B	16	180	60	120	2,040	940	1,167	0.98
R H	17	160	80	100	1,820	845	1,249	0.92
J D	18	210	120	150	2,670	1,175	2,004	1.05
N R	19	160	80	100	1,860	1,064	1,032	1.15
J M	20	120	70	120	1,840	791	1,446	1.04
Z J	21	160	80	140	2,220	964	1,681	1.00
R C	22	110	70	90	1,530	760	1,351	1.05
A M	23	200	80	135	2,335	977	1,553	2.87
W R	24	175	75	100	1,900	996	1,474	1.00
C P	25	165	70	140	2,200	878	1,213	1.02

as reliable as can be obtained from patients not under complete hospital supervision. The average daily intake of thiamine and riboflavin, as shown in table 5 for each patient, was calculated on the basis of the food content as given by Williams and Spies⁵ for thiamine and by Fixsen and Roscoe⁶ for all riboflavin except that derived from meats. For

⁴ The patients received 30 cc of the extract three times a day, although the usual dose is only 30 cc daily. The alcohol content of the extract may possibly have accounted for some of the increased sense of well-being.

⁵ Williams, R. R., and Spies, T. D. *Vitamin B₁ and Its Use in Medicine*. New York, The Macmillan Company, 1939.

⁶ Fixsen, M. A., and Roscoe, M. H. *Tables of the Vitamin Content of Human and Animal Foods*, Nutrition Abstr. & Rev. **7**: 823-867, 1938.

meats we used the riboflavin values given by Mickelsen, Waisman and Elvehjem⁷

If 600 Bourquin-Sherman units of riboflavin represent the normal person's daily need⁸ and if 1 such unit is taken as equivalent to 3 micrograms, which are the values used in our calculation, it is seen (table 5) that most of our patients were receiving less than the normal 1.8 mg of riboflavin daily. Their thiamine intake was also below the 1 mg daily estimated by Williams and Spies as a crude minimal requirement. Requirement calculations are usually made on the basis of a 3,000 calory diet, however, while the diets of our patients ranged from 1,040 to 2,670 calories, with an average caloric value of only 1,805. If there does exist a quantitative relation between the rate of combustion and the vitamin requirement, then the dietary thiamine and riboflavin intake of our

TABLE 6—*Normal Improvement in Diabetic State Under Continuous Control*

Patient	Diet, Gm			Insulin Requirement								
	Carbohy- drate	Pro- tein	Fat	At Be- Begin- ning	1 Week	2 Weeks	4 Weeks	6 Weeks	8 Weeks	10 Weeks	4 Months	1 Year
A H	120	80	70	35	30	25	20	10	0	0	0	0
L B	100	60	60	75	75	75	50	40	40	40	40	40
H G	140	80	125	27	25	25	20	18	15	10	0	0
N B	100	60	120	30	30	25	20	10	0	0	0	0
M D	100	70	100	54	50	50	40	30	25	15	0	0
J S	200	80	125	45	35	35	35	30	20	15	15	15
R H	225	66	100	60	50	35	30	30	30	30	30	†
W C	170	70	100	75	50	50	50	40	30	20	20	20
W I	200	80	100	80	75	70	60	50	50	50	40	40
D J	100	60	50	32	30	25	15*	15	5	0	0	0

* Did not continue cooperation

† Diet increased to 160 Gm of carbohydrate, 75 Gm of protein and 80 Gm of fat

patients was probably at a safe and adequate level. Our ratios of thiamine to nonfat calories in the diets average much above the normal value of 0.5 as given by Williams and Spies.

In the one paper (by Sindoni⁹) referred to by Williams and Spies as indicating a vitamin inadequacy in diabetic diets, there are found no quantitative data whatever as to the dietary intake of vitamins. Here again, uncontrolled diabetic patients who had previously been on

7 Mickelsen, O., Waisman, H. A., and Elvehjem, C. A. Recent Studies on the Vitamin Content of Meats and Meat Products, *J Am Dietet A* **15** 529-536, 1939

8 Daniel, E. P., and Munsell, H. E. Vitamin Content of Foods, Miscellaneous Publication 275, United States Department of Agriculture, 1937

9 Sindoni, A., Jr. Vitamin Deficiency in Prescription Diets of Diabetics. Study into Relationship of Diet Deficiency to Symptomatology as Observed in Eighty-Five Diabetics with Previous Dietary Treatment, *Am J Digest Dis & Nutrition* **3** 750, 1936

unknown diets presumably inadequate in vitamin content showed symptomatic improvement and lessened insulin need after being placed under proper dietary and insulin control. This improvement Sindoni attributed to an increased intake of vitamins in the form of green vegetables and citrus fruits, but we point out the well known fact (table 6) that such improvement in the diabetic state regularly accompanies the placing of patients under proper dietary and insulin control alone.

COMMENT ON RESULTS

From the data here presented, there is found no evidence of benefit from thiamine or riboflavin therapy for well controlled diabetic patients except in the treatment of diabetic neuritis. Nor is there any obvious deficiency of these two vitamin factors in ordinary diabetic diets. Previously recommended vitamin therapy for diabetes would thus seem to be without basis in fact. Recommendations of such therapy have mainly been based on clinical testing of patients not adequately controlled before the tests were begun. In table 6 is shown the marked improvement diabetic patients exhibit in their ability to use dextrose, as their diabetic state is properly controlled through the months only by diet and insulin. They regularly show a reduction in insulin need as the months of adequate control pass. Eventually a basic level is reached for most adult diabetic patients—a level of insulin and dietary need at which they are maintained for long periods without change unless infection or other intercurrent disease disrupts their established balance.

In only 1 of our 25 patients who received the vitamin therapy was there any marked reduction in insulin need, and this patient was the only one not adequately standardized before the vitamin therapy was begun. Obviously our results have no bearing on the use of vitamin therapy in cases of uncontrolled diabetes or in conjunction with diet and insulin from the beginning of treatment. The urinary loss of large amounts of dextrose in cases of uncontrolled diabetes may perhaps lead to a vitamin depletion, but this has so far not been shown for any vitamin B fractions. Our results indicate only that in cases of well controlled diabetes there appears to be no need for thiamine or riboflavin beyond the amounts present in ordinary diabetic diets, except in the case of diabetic neuritis. On this condition thiamine seems to exert almost a specific effect. The fact that in most cases of such neuritis improvement also occurs when the diabetic state is brought under proper control by diet and insulin might suggest a thiamine deficiency during the uncontrolled period, but there also exists the possibility that the improvement in neuritis results only from increased tissue combustion of sugar under insulin therapy and not from a specific lack of thiamine.

Our negative results with thiamine and riboflavin therapy may be criticized by some investigators on account of the relatively small amounts given. Such criticism would be justified if we had admin-

istered the vitamins only for short periods. But when the vitamins are given for several months in amounts two or three times the normal minimal daily requirement and in addition to an adequate dietary supply, there would seem to be little doubt that any vitamin deficit in the body tissues will have been covered.

The possibilities of vitamin C inadequacy in cases of uncontrolled diabetes or of therapeutic use of the vitamin in conjunction with the usual dietetic and insulin management of the disease are at present under investigation.

Actual and severe vitamin deficiency may play a part in one important complication—diabetic coma. In this condition food and vitamin intake ceases, usually in the presence of a fever which causes heightened combustion. Nor do the usual methods of treatment of coma provide for any replenishment of vitamins. The most severe evidences of damage due to coma occur in those tissues with the highest rate of combustion and hence with the greatest need for the vitamin B fractions—the brain, the kidney and the heart muscle. We are at present investigating this phase of diabetic coma with a view to adding intensive vitamin therapy to our usual treatment of such coma. Certainly diabetic coma still presents an unsolved clinical problem, with a fatality rate as high as in the early days of insulin therapy.

CONCLUSIONS

- 1 Usual diabetic diets, as routinely used for our patients, contain adequate amounts of thiamine and riboflavin in relation to their total caloric value.

- 2 Administration of large amounts of thiamine and riboflavin to well controlled diabetic patients over many weeks does not reduce the insulin requirement or alter the severity of the diabetic state.

- 3 In cases of well controlled diabetes there seems no need for thiamine or riboflavin beyond the amounts provided by ordinary diabetic diets. This holds true except for patients suffering from diabetic neuritis, a condition in which thiamine therapy seems to result in prompt improvement or cessation of the neuritic symptoms.

- 4 Dextrose tolerance regularly increases in diabetic patients as their diabetic state is controlled by diet and insulin through the first few months. Many of the claims of benefit from vitamin therapy have been based on clinical testing carried out on patients before they had been brought under proper control by diet and insulin or before they had reached a stable state.

Dr C. A. Mills gave constructive suggestions and criticism during the study and in the preparation of the manuscript.

The thiamine was supplied by Eli Lilly & Co., and the riboflavin by Merck & Co., Inc.

PANCREATIC SECRETION IN MAN AFTER STIMULATION WITH SECRETIN AND ACETYLBETAMETHYLCHOLINE CHLORIDE

A COMPARATIVE STUDY

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Secretory activity of the pancreas may be stimulated by either a humoral (secretin) or a neural (vagal) mechanism. The amount and type of secretion produced by the two mechanisms has been shown to differ widely in animals. Stimulation with secretin produces a large volume of pancreatic juice rich in bicarbonate and poor in enzymes, whereas vagal stimulation produces a scant flow of juice poor in bicarbonate and rich in enzymes. Mellanby¹ hypothesized that the content of enzymes in the pancreatic juice is determined by action of the vagus nerves, whereas the concentration of the bicarbonate solution in which these enzymes are contained is determined by the action of secretin. In a clinical study of pancreatic function, the response of the pancreas to both types of stimulants should be determined in order to obtain a complete picture.

In man, the effect of intravenous injection of purified secretin was first studied, in 1926, by Chiray, Salmon and Mercier². They reported an increase in the amount of juice obtained by means of an Einhorn duodenal tube, as well as an increase in the concentration of trypsin and lipase. Voegtlin, Greengard and Ivy,³ in 1934, reported an extensive investigation of the effects in man of intravenous injections of secretin prepared by Ivy. They showed that the volume of secretion and the total output of enzymes increased during the first fifteen minutes after

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1 Mellanby, J. The Mechanism of Pancreatic Digestion—The Function of Secretin, *J Physiol* **60** 85-91 (May) 1925

2 Chiray, M., Salmon, A. R., and Mercier, A. Action de la sécrétine purifiée sur la sécrétion externe du pancréas de l'homme, *Bull et mém Soc med d hôp de Paris* **50** 1417-1426 (July 30) 1926

3 Voegtlin, W. L., Greengard, H., and Ivy, A. C. The Response of the Canine and Human Pancreas to Secretin, *Am J Physiol* **110** 198-224 (Nov) 1934

injection but that the concentration of enzymes did not decrease or increase consistently. In 1936, Chiray and Bolgert⁴ published the results of an extensive investigation in which it was shown that the volume of pancreatic juice and the total quantity of enzymes increased after administration of secretin intravenously. A year later, Ågren and Lagerlof⁵ reported their results with secretin prepared by Hammeisten and Ågren, they found that when injected intravenously secretin produced a rapid increase in the volume of secretion and a rise in the concentration of bicarbonate therein contained, whereas the concentration of the enzymes amylase and trypsin fell. This indicated a washing out of the preformed enzymes stored in the pancreatic system, followed by secretion of the recently formed enzymes, for the most part sustained at a lower level of concentration. A large quantity of enzyme was excreted during the first ten minutes.

Ågren and Lagerlof devised a double tube, one lumen was used to keep the stomach free of secretion and the other to aspirate the duodenal contents. By this means they prevented the entrance of gastric contents into the duodenum, avoided the admixture of gastric and duodenal contents and thus obtained much greater accuracy in the analysis of the duodenal contents than had previously been possible. In the United States, Diamond, Siegel, Gall and Karlen,⁶ using the same method and the same secretion, have confirmed recently the results of Ågren and Lagerlof.

Although the drugs which act as stimulants of the parasympathetic nervous system have been used frequently to study the effect of vagal stimulation on pancreatic secretion in animals, references to their use for this purpose in man are not numerous. Pilocarpine is reported⁷ as having both increased and decreased⁸ the rate of secretion, physostigmine increases the rate, as does mecholyl chloride. These

4 Chiray, M., and Bolgert, M. Mesures de la sécrétion pancréatique externe en clinique par l'épreuve à la sécrétine purifiée, *Nutrition* **6**:223-230, 1936.

5 Ågren, G., and Lagerlof, H. The Pancreatic Secretion in Man After Intravenous Administration of Secretin, *Acta med. Scandinav.* **90**:1-29, 1936.

6 Diamond, J. S., Siegel, S. A., Gall, M. B., and Karlen, S. The Use of Secretin as a Clinical Test of Pancreatic Function, *Am. J. Digest. Dis.* **6**:366-372 (Aug.) 1939.

7 Holsti, O. Beiträge zur Kenntnis der Pankreassekretion beim Menschen, *Deutsches Arch. f. klin. Med.* **111**:48-92 (June) 1913. Snyder, W. H., Jr., and Lum, R. Pancreatic Fistula. A Case with Intubation of Wirsung's Duct, *Surg., Gynec. & Obst.* **62**:57-64 (Jan.) 1936. Villaret, M., and Justin-Besançon, L. Étude clinique et physiologique d'une fistule pancréatique, *Arch. d. mal. de l'app. digestif* **15**:751-767 (Oct.) 1925.

8 McCaughan, J. M., Sinner, B. L., and Sullivan, C. J. The External Secretory Function of the Human Pancreas. Physiologic Observations, *Arch. Int. Med.* **61**:739-754 (May) 1938.

reports pertain to the effects of the drugs on patients who had external pancreatic fistulas. Loeper, Lemaire and Dany⁹ used acetylcholine as a stimulant of pancreatic function in a few cases, they obtained the duodenal contents by the use of a duodenal tube. Detailed data on the effect of drugs that stimulate the parasympathetic nervous system on external pancreatic secretion are apparently not available.

The purpose of this investigation was (1) to obtain further data on the action of secretin in man, particularly in regard to p_H values and to lipase, (2) to study the effect of parasympathetic stimulants on external pancreatic secretion in man, (3) to compare the amount and quality of secretion produced after vagal stimulation with that produced after stimulation with secretin, and (4) to develop a method by means of which pancreatic secretion produced by vagal stimulation might be studied clinically.

EXPERIMENTAL METHOD

After the subject had experienced a twelve hour fast, a double tube, devised by Ågren and Lagerlof, was introduced into the duodenum, it was allowed to descend until bile was recovered from both the gastric and the duodenal lumens. The tube then was withdrawn slowly until gastric juice was flowing from the gastric lumen of the tube and duodenal contents from the duodenal lumen of the tube. The position of the tube was determined by roentgen examination.

Continuous aspiration with a negative pressure of 16 to 25 inches (40.5 to 63.5 cm) of water was carried out. This negative pressure was found to be sufficient for the prevention, to a great extent, of the overflow of gastric juice into the duodenum and for the collection of duodenal contents.

The duodenal contents were studied in four ten minute periods before stimulation and into four ten minute periods and two twenty minute periods after stimulation. The effect of various positions on aspiration was studied, a position was finally adopted in which the patient was half reclining on his back.

A purified secretin was used, 1 clinical unit for each kilogram of body weight was injected intravenously. Acetylbetamethylcholine chloride (mecholyl chloride) was chosen from among the parasympathetic stimulants. After numerous trials, it was found that 15 mg. given subcutaneously usually produced a measurable effect on pancreatic secretion, doses greater than 15 mg. tended to stimulate gastric secretion so greatly that entrance of the gastric contents into the duodenum was difficult to prevent.

Fourteen normal subjects were used. Twenty experiments with secretin as a stimulant were carried out on 13 of the 14 subjects, and 22 experiments with mecholyl chloride were carried out on 10 of the 14 subjects. A single test with secretin as a stimulant was carried out on 7 subjects, two tests on 5 subjects and three tests on 1 subject. With mecholyl chloride as a stimulant a single test was carried out on each of 5 subjects, two tests on each of 2 subjects, three tests on 1 subject, five tests on 1 subject, and seven tests on 1 subject.

Cloudiness of the duodenal contents indicated admixture of gastric contents. All clouded fractions were discarded. Entrance of the gastric contents into the

9 Loeper, M., Lemaire, A., and Dany, H. Influence de l'atropinisation sur la response vesiculaire a l'acetylcholine, *Compt rend Soc de biol* **113** 1478-1479, 1933.

duodenum occurred infrequently but occurred more often when mecholyl chloride was used as a stimulant than when secretin was so used. Spilling over of the acid gastric contents occurred most frequently with subjects who had hyperacidity.

CHEMICAL METHODS

Hydrogen ion concentration (p_H) was determined by the quinhydrone-electrode method. Amylase activity was determined by the method of Norby¹⁰ as modified by Ågren and Lagerlof. Determinations of the activity of trypsin were carried out by the procedure given by Ågren and Lagerlof, which is the method outlined by Willstatter, Waldschmidt-Leitz, Dünaturria, and Kunstner¹¹ and modified by Christiansen¹². The activity of lipase was determined by the method of Crandall and Cherry,¹³ as reported by us in previous studies, with a 1:10 dilution of specimens from the duodenum.¹⁴

EXPERIMENTAL DATA

If more than one test was carried out on a single subject, the average result of all the tests done on that person is given in tables 1, 2, 3, 4 and 5. The data presented in the tables are based on too few experiments to give precise means and extremes. However, analysis of individual cases will show that the averages depict the behavior of the various factors studied. Averages have been used in construction of the curve represented in charts 1 to 8.

Volumes of content recovered in control tests on the same person showed remarkable agreement, considering the technical difficulties involved in removing the duodenal contents quantitatively. Thus, in the first ten minute period after stimulation with secretin, the volumes were 18 and 24 cc in 1 case, 34, 32 and 62 cc in a second case, 48 and 53 cc in a third case, and 25 and 20 cc in a fourth case. The volumes in the first forty minute period following stimulation with secretin in the same cases were, respectively, 93 and 93 cc, 156, 233 and 203 cc, 111 and 128 cc, and 135 and 95 cc. A somewhat greater variation in the volumes was obtained after stimulation with mecholyl chloride. The p_H values as well as the values for several enzymes were likewise comparatively constant for the same subject after stimulation.

Effect of Stimulation on the Gross Appearance of Duodenal Contents—After the injection of secretin the volume of duodenal contents recovered increased markedly. The effect of this was noticeable within a short period, usually a minute, the normal biliary color of the duodenal contents rapidly became less marked,

¹⁰ Norby, cited by Ågren and Lagerlof.⁵

¹¹ Willstatter, R., Waldschmidt-Leitz, E., Dünaturria, S., and Kunstner, G. Zur Kenntnis des Trypsin. XV. Abhandlung über Pankreasenzyme, *Ztschr. f. physiol. Chem.* **161**: 191-210, 1926.

¹² Christiansen, T. Kliniske Studier over den digestive Duodenalsaftsekretion. Samt et Bidrag til Spørgsmaalet om den exokrine Pankreasfunktion ved Achylia gastrica, Copenhagen, Levin & Munksgaard, 1933.

¹³ Crandall, L. A., Jr., and Cherry, I. S. Presence of an Olive Oil Splitting Lipase in the Blood of Patients with Multiple Sclerosis, *Proc. Soc. Exper. Biol. & Med.* **28**: 572-574 (March) 1931.

¹⁴ Comfort, M. W., Parker, R. L., and Osterberg, A. E. The Concentration of Pancreatic Enzymes in the Duodenum of Normal Persons and Persons with Disease of the Upper Part of the Abdomen, *Am. J. Digest. Dis.* **6**: 249-254 (June) 1939.

and in many instances a clear, almost colorless secretion was obtained. The yellowish color reappeared, however, after a short time.

After administration of mecholyl chloride there was a slight increase in volume, and in many instances dark bile appeared soon after injection of the drugs, indicative of emptying of the gallbladder.

Volume of Duodenal Contents—Before stimulation the volume of duodenal contents varied from 1 to 20 cc, the average being 8.78 cc for a ten minute period (table 1). After stimulation with secretin the volume increased markedly in every instance, being greater in the first ten minute period after stimulation than during any ten minute period before stimulation (more than 20 cc, with an average of 39 cc). The greatest volume was recovered in 9 cases in the first, in 3 cases in the second and in 1 case in the third ten minute period. The increase in the first ten minute period ranged from one-half to tenfold, averaging fourfold.

TABLE 1—*Volume of Duodenal Contents Before and After Stimulation with Secretin and Mecholyl Chloride*

Case	Before Secretin, 10 Minute Periods		After Secretin						Before Mecholyl Chloride 10 Minute Periods		After Mecholyl Chloride					
			10 Minute Periods			20 Minute Periods					10 Minute Periods			20 Minute Periods		
	2	1	1	2	3	4	5	6	2	1	1	2	3	4	5	6
1	20	—	32	18	—	—	20	14	—	—	—	—	—	—	—	—
2	12	14	21	21	34	24	30	20	9	11	20	32	20	5	15	13
3	8	13	43	49	53	43	60	34	14	19	26	24	38	14	19	18
4	—	—	—	—	—	—	—	—	8	7	7	6	21	11	9	65
5	3	8	63	18	15	25	50	16	—	—	—	—	—	—	—	—
6	10	18	50	19	15	34	31	12	10	4	14	10	5	4	11	5
7	3	1	22	29	28	35	40	32	2	7	7	10	4	1	0.5	3
8	6	—	46	34	25	27	29	10	7	7	18	8	—	7	11	—
9	10	13	31	24	47	21	9	5	—	—	—	—	—	—	—	—
10	7	11	32	29	29	25	26	39	—	—	—	—	—	—	—	—
11	—	—	44	23	21	24	6	—	—	8	18	3	5	13	6	5
12	—	—	32	30	20	18	44	—	—	2	—	—	8	5	17	—
13	4	6	37	22	19	12	27	19	5	4	14	—	2	—	6	4
14	11	7	52	23	28	17	38	—	7	7	13	11	14	10	3	2
Average	7.0	10.2	39.0	26.1	27.9	25.5	31.6	—	7.9	7.8	14.5	13.2	13.1	7.8	9.8	40.8
Range	3.0	1.5	21	18-	15	12	6	5	2.5	2.5	7-	3	2	1	0.5	2
	20.0	18.0	52	48.7	53	43	59.7	33.7	13.8	18.8	26	31.6	38.3	13.9	18.8	65

After the maximal degree of increase there was usually a slight fall, but the volume usually was maintained at a level much greater than that which existed before stimulation. The volume declined thereafter, reaching prestimulation levels in sixty to eighty minutes.

After stimulation with mecholyl chloride, the volume of secretion rose in 8 subjects but was maintained at its prestimulation levels in 2 (table 1). The greatest rise occurred in 4 cases in the first, in 2 cases in the second and in 4 cases in the third ten minute period. At some time during the forty minute period after stimulation, the volume increased from one to threefold. The small increase in volume after administration of mecholyl chloride is in contrast with the great increase that occurred after secretin was given (chart 1).

Hydrogen Ion Concentration of Duodenal Contents—Before stimulation, the hydrogen ion concentration varied between 6.35 and 7.78, the average was 7.05 (table 2). After stimulation with secretin, a definite increase in hydrogen ion concentration occurred in every case. In all cases a rise of at least 1 p_H unit occurred, in 12 of the 13 subjects a p_H of at least 8 was reached after stimulation.

with secretin. On the other hand, after stimulation with mecholyl chloride there was no significant change in the hydrogen ion concentration. In chart 2 the contrasting tendencies after stimulation with secretin and mecholyl chloride are illustrated.

Concentration of Amylase in Duodenal Contents—Before stimulation, the concentration of amylase in terms of grams of maltose liberated per cubic centimeter of duodenal contents varied from 1.03 to 3.10 Gm, averaging 1.3 Gm (table 3). After stimulation with secretin, the concentration of amylase rose in 6 subjects, fell in 5 subjects and remained unchanged in 2 subjects in the first ten minute period. The response was entirely different in the second ten minute period, during which a fall in concentration occurred in all 13 cases (100 per cent), reaching a level below that found before stimulation in each person studied. The concentration decreased to less than 0.6 Gm in every case and to less than 0.5 Gm of maltose per cubic centimeter of duodenal contents in 10 of the 13 cases. The

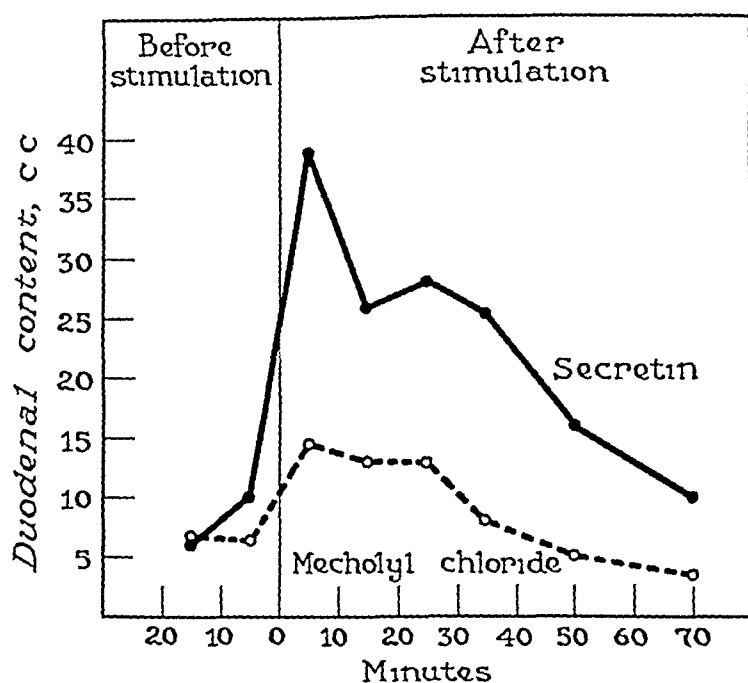


Chart 1—Average volume of duodenal contents per unit of time before and after stimulation with secretin and mecholyl chloride

concentration remained below prestimulation levels in 8 of 10 cases during the third and fourth ten minute periods. The lowest concentration was found in 12 of the 3 cases in the second ten minute period and in 2 of the 13 in the third. Although the concentration tended to remain below the prestimulation levels, a rise occurred above that of the second ten minute period in 8 of 10 cases in the third ten minute period and above that of the third period in 8 of 10 cases in the fourth ten minute period. The concentration did not return to prestimulation levels during the eighty minutes in 9 cases but did return to the prestimulation levels once in the thirty to forty minute period and twice in the forty to sixty minute period. In other words, secretin produces a prolonged depression of the concentration lasting forty to eighty minutes or longer, which is greatest in the second ten minute period and is followed by a slight secondary rise which may or may not reach prestimulation levels in eighty minutes.

The effect of stimulation with mecholyl chloride is strikingly different from that of stimulation with secretin (table 3). After stimulation with mecholyl chloride the concentration increased in every case during the first ten minute period, the maximal concentration was obtained in 2 cases in the first, in 2 cases in the second, in 2 cases in the third and in 3 cases in the fourth ten minute period and in 1 case in the forty to sixty minute period. In 9 of the 10 cases a concentration of more than 37 Gm of maltose per cubic centimeter of duodenal contents was reached, whereas a concentration of more than 4 Gm of maltose per cubic centimeter of duodenal contents was reached in 8 of the 10 cases and more than 5 Gm of maltose in 4 of 10 cases. A concentration greater than prestimulation levels was maintained for forty minutes in all 10 cases, for sixty minutes in 8 of 10 cases and for eighty minutes in 7 of 9 cases. In short, a prolonged rise in concentration occurs after stimulation with mecholyl chloride that persists for sixty to

TABLE 2— P_H Values of Duodenal Contents Before and After Stimulation with Secretin and Mecholyl Chloride

Case	Before Secretin, 10 Minute Periods		After Secretin						Before Mecholyl Chloride 10 Minute Periods		After Mecholyl Chloride					
			10 Minute Periods				20 Minute Periods				10 Minute Periods				20 Minute Periods	
	2	1	1	2	3	4	5	6	2	1	1	2	3	4	5	6
1	65	—	76	86	—	—	82	82	—	—	—	—	—	—	—	—
2	67	72	78	83	77	75	76	75	74	73	71	71	70	79	72	73
3	70	71	78	81	79	79	79	80	74	72	73	72	74	74	75	75
4	—	—	—	—	—	—	—	—	77	78	78	78	77	79	77	77
5	—	74	77	77	82	79	73	78	—	—	—	—	—	—	—	—
6	74	69	78	83	83	79	77	79	67	70	72	72	71	73	66	60
7	65	67	76	80	80	71	70	70	71	66	71	71	73	71	70	68
8	64	—	74	81	79	80	77	79	72	69	73	72	—	66	65	—
9	65	64	74	75	71	73	72	72	—	—	—	—	—	—	—	—
10	70	70	77	82	81	81	80	79	—	—	—	—	—	—	—	—
11	—	65	77	79	81	74	77	—	—	73	74	71	71	82	71	82
12	—	—	72	79	79	79	74	—	—	67	—	—	69	78	64	—
13	69	71	79	82	82	82	79	75	76	75	73	72	—	70	—	77
14	73	74	79	81	82	82	81	—	76	77	72	74	74	73	77	78
Average	683	696	765	808	798	780	767	768	734	721	730	727	724	747	707	738
Range	64	64	72	75	71	71	70	69	67	66	71	71	69	66	64	68
	74	74	79	86	83	81	82	82	77	77	78	78	74	79	77	82

eighty minutes or longer. The contrasting responses to the two types of stimulants are represented in chart 3.

Amylase Value per Total Sample—Before stimulation, the total value for amylase in terms of grams of maltose liberated by all the duodenal contents recovered per ten minute period varied from 1.12 to 54.07 Gm, an average of 10.8 Gm (table 3). After stimulation with secretin, a rapid increase in the total amylase in terms of grams of maltose liberated from the first ten minute fraction of duodenal contents occurred in 12 of 13 cases. The increase varied from a fraction to fourteenfold and averaged fourfold. In 12 of the 13 cases the total amylase varied from 10 to 70 Gm of maltose, the maximal value per ten minute period occurred in the first period in 12 of the 13 cases. The rapid increase in the total amylase in the first ten minute period was followed by a rapid fall in the second ten minute period in all cases, in 7 of 11 cases it decreased to levels less than those obtained before stimulation. The fall usually was followed by a slight rise in the third and fourth ten minute periods which persisted during the first twenty minute period, but it is to be noted that the total value was only slightly greater than prestimulation levels in the third and fourth ten minute period and the first twenty

minute period. Although there is a diminution in concentration after stimulation with secretin, the total value for amylase is increased. It is significant that the total value for amylase per ten minute period was increased in 12 of 13 cases only during that ten minute period following stimulation, when the concentration was not decreased and the volume was largest after stimulation. As soon as the concentration fell (second ten minute period), the total value fell in spite of the persistent secretion of large volumes. The large total value for amylase in the first ten minute period has resulted from the washing out of the enzyme in the cells, not from stimulation of the cell.

After stimulation with mecholyl chloride an increase in total amylase occurred in all 10 cases (table 3). The increase varied from twofold to tenfold and averaged fourfold. In 5 of 9 cases the total value was 70 Gm of maltose per ten minute fraction of duodenal contents, a value greater than that usually attained after stimulation with secretin. Although the rise was well sustained, the maximal

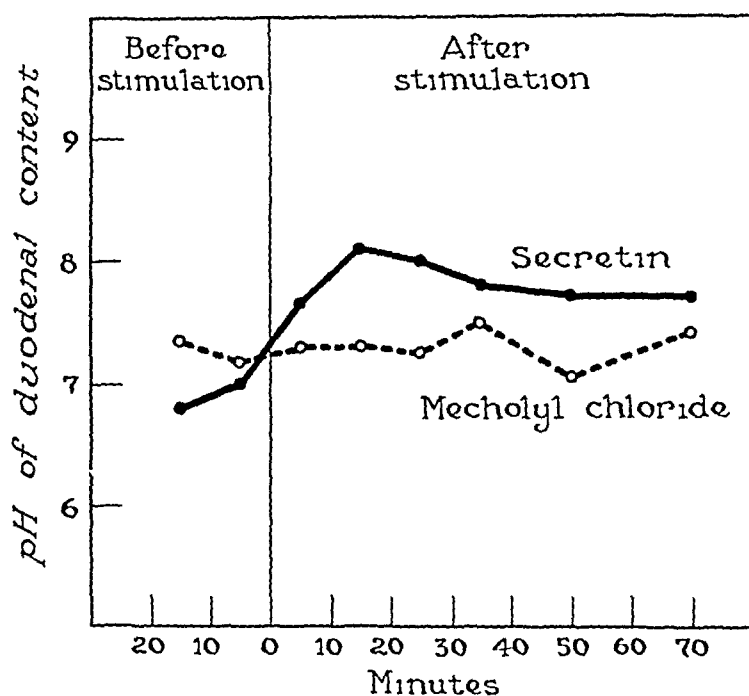


Chart 2—Average pH of samples of duodenal contents per unit of time before and after stimulation with secretin and mecholyl chloride

value occurred in 4 cases in the first period, in 2 cases in the second, in 2 cases in the third and in 2 cases in the fourth period, the total value per unit period returning to prestimulation levels in 1 instance in twenty to thirty minutes, in 2 instances in thirty to forty minutes, in 1 instance in forty to sixty minutes and in 3 instances in sixty to eighty minutes but persisting beyond eighty minutes in the remaining 4 cases. Mecholyl usually produces a prolonged, sustained rise in the total value for amylase, contrasting with the sharp rise and rapid fall characteristic of the influence of secretin on the total amylase per unit period (chart 4).

Concentration of Trypsin.—Before stimulation, the concentration of trypsin, in terms of cubic centimeters of tenth-normal potassium hydroxide per cubic centimeter of duodenal contents, varied from 0.6 to 3.2 cc, averaging 1.60 cc (table 4). After stimulation with secretin the concentration fell in 8 cases and rose in 4 cases in the first ten minute period. A fall occurred in 13 cases (100 per cent) in the second

TABLE 3—Concentration of Amylase Before and After Stimulation with Secretin and Mecholyl Chloride (Grams Maltose per Cubic Centimeter of Duodenal Contents)

Case	After Secretin										After Mecholyl Chloride									
	Before Secretin, 10 Minute Periods		10 Minute Periods				20 Minute Periods				Before Mecholyl Chloride, 10 Minute Periods		10 Minute Periods				20 Minute Periods			
	2	1	1	2	3	4	5	6			2	1	1	2	3	4	5	6		
1	1.03	1.72	1.72	0.26	—	—	1.38	1.38			1.44	1.17	2.75	3.47	3.44	4.82	4.13	2.28		
2	1.12	0.69	0.69	0.39	0.86	0.52	1.55	0.86			2.21	3.10	4.13	5.43	4.82	3.75	2.92	2.92		
3	1.67	1.58	1.58	0.55	0.86	0.77	1.09	1.52			0.52	1.72	2.06	3.44	4.47	2.75	3.78	3.44		
4	1.72	1.03	1.03	0.26	0.34	0.69	1.03	0.69			0.86	0.86	1.03	1.46	2.67	2.75	3.78	0.52		
5	0.47	0.52	0.43	0.15	0.21	0.47	0.30	0.34			1.63	1.51	4.17	3.10	3.78	4.82	2.92	2.24		
6	1.03	0.69	0.69	0.34	0.28	0.56	0.82	0.52			1.38	1.03	3.10	2.84	—	—	3.10	—		
7	1.55	0.77	0.77	0.43	0.69	0.43	0.69	0.95			—	0.86	1.03	1.46	—	—	—	—		
8	0.69	1.03	1.03	0.26	0.30	0.52	0.43	0.30			—	0.86	1.72	1.55	5.50	5.85	5.85	5.16		
9	0.77	0.52	0.69	0.04	0.13	0.09	0.19	0.26			—	1.03	6.19	5.68	1.03	1.72	1.03	0.52		
10	—	—	1.46	0.60	0.95	1.03	1.55	—			—	0.86	1.72	1.55	5.50	5.85	5.85	5.16		
11	—	—	0.69	0.26	0.17	0.69	0.86	—			—	1.03	—	—	1.03	1.72	1.03	—		
12	0.34	0.34	0.77	0.09	0.34	0.52	1.12	1.20			1.72	2.24	6.19	5.68	—	3.78	—	—		
13	1.38	1.20	1.89	0.52	0.52	0.52	0.86	—			2.58	1.89	4.18	5.68	1.47	4.64	4.13	3.44		
14	1.067	0.952	1.034	0.318	0.471	0.566	0.889	0.801			1.543	1.540	3.293	3.637	3.774	3.790	3.517	2.725		
Average	1.03	0.34	0.43	0.04	0.13	0.09	0.19	0.26			0.52	0.86	1.03	1.46	1.03	1.72	1.03	0.52		
Range	1.72	1.69	1.89	0.60	0.95	1.03	1.55	1.52			2.58	3.10	6.19	5.68	5.51	5.85	5.85	5.16		
Total Values of Amylase Before and After Stimulation with Secretin and Mecholyl Chloride (Grams Maltose per Total Sample)																				
1	20.64	55.04	55.04	4.64	—	—	27.52	19.26			13.07	14.79	56.15	106.38	75.70	24.09	58.83	36.46		
2	13.42	16.86	14.44	7.87	20.64	12.38	47.82	22.05			26.78	54.07	108.13	125.80	112.45	51.26	37.79	45.41		
3	13.07	22.42	59.51	26.40	45.53	33.28	61.61	55.10			4.13	12.04	14.45	22.37	93.95	30.27	34.06	22.86		
4	—	—	—	—	—	—	—	—			—	—	—	—	—	—	—	—		
5	5.16	11.01	65.02	4.64	5.16	17.20	51.60	11.01			8.60	4.13	19.95	17.98	12.53	11.87	41.62	4.13		
6	5.08	9.29	21.50	2.84	2.79	16.51	9.93	5.24			3.61	7.22	33.56	31.99	18.65	3.01	1.46	6.71		
7	3.10	1.12	15.77	10.15	7.74	19.91	20.64	16.51			9.64	7.91	57.28	22.02	—	33.73	31.06	—		
8	9.29	—	35.13	15.48	16.63	11.78	17.89	9.20			—	—	—	—	—	—	—	—		
9	6.88	13.42	31.09	6.19	14.15	10.81	3.87	1.50			—	—	—	—	—	—	—	—		
10	5.42	5.68	22.02	1.25	3.74	2.15	5.02	10.06			—	—	—	—	—	—	—	—		
11	—	—	61.76	13.84	12.06	14.25	9.29	—			—	6.88	30.96	1.64	27.53	76.05	35.10	25.81		
12	—	—	22.26	7.74	3.44	12.38	37.84	—			—	2.85	—	—	8.26	8.60	17.54	—		
13	1.38	2.34	27.53	1.89	6.54	6.19	30.19	22.58			0.46	8.95	85.69	45.41	—	11.35	—	—		
14	15.14	8.43	98.38	11.87	14.45	8.77	32.08	—			18.07	13.24	53.66	62.44	62.64	46.44	12.38	0.88		
Average	8.96	10.06	41.06	8.83	12.75	13.80	27.61	17.34			11.67	13.18	51.09	48.78	51.47	29.67	30.32	19.67		
Range	1.38	1.12	14.44	1.25	2.79	2.15	3.87	1.50			4.13	2.58	14.45	4.61	8.26	3.01	1.46	1.13		
	20.64	22.42	98.38	26.40	45.53	33.28	61.61	55.70			26.78	54.07	108.13	106.38	112.45	76.05	58.83	36.46		

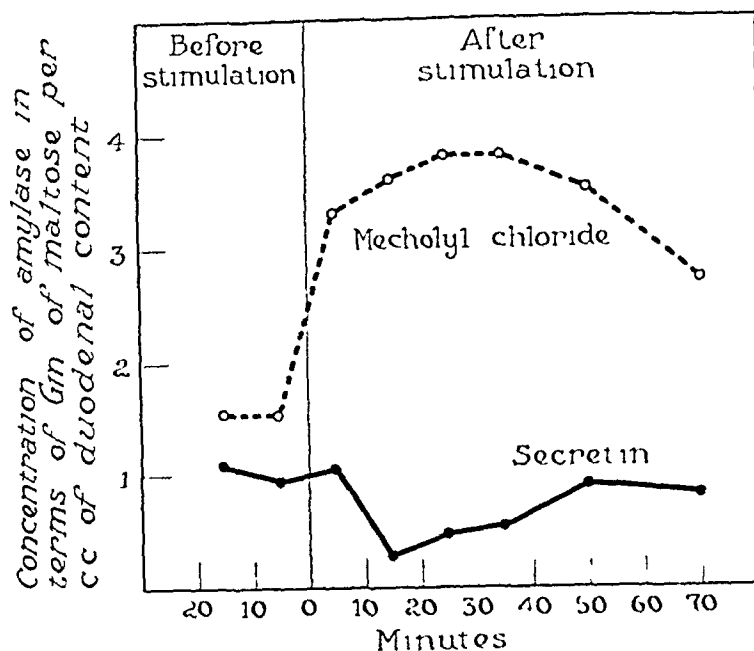


Chart 3—Average concentration of amylase per cubic centimeter of duodenal contents in a sample obtained per unit of time before and after stimulation with secretin and mecholyl chloride

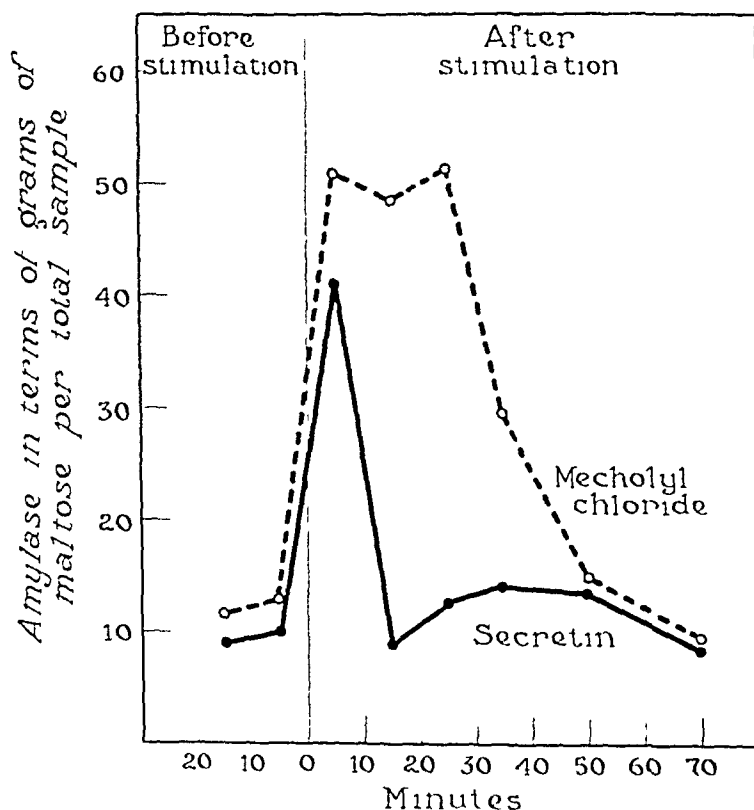


Chart 4—Average value for total amylase per total sample obtained per unit of time before and after stimulation with secretin and mecholyl chloride

TABLE 3—Concentration of Amylase Before and After Stimulation with Secretin and Mecholyl Chloride (Grams Maltose per Cubic Centimeter of Duodenal Contents)

Case	After Secretin										After Mecholyl Chloride									
	Before Secretin, 10 Minute Periods		10 Minute Periods				20 Minute Periods				Before Mecholyl Chloride, 10 Minute Periods		10 Minute Periods				20 Minute Periods			
	2	1	1	2	3	4	5	6			2	1	1	2	3	4	5	6		
1	1.03	1.72	1.03	0.26	—	—	1.38	1.38			1.44	1.17	2.75	3.47	3.44	4.82	4.13	2.28		
2	1.12	1.20	0.69	0.39	0.86	0.52	1.55	0.86			2.21	3.10	4.13	5.43	4.82	3.75	2.92	2.32		
3	1.67	1.69	1.58	0.55	0.86	0.77	1.09	1.52			0.52	1.72	2.06	3.44	4.47	2.75	3.78	3.44		
4																				
5	1.72	1.33	1.03	0.26	0.34	0.69	1.03	0.69			0.86	0.86	1.03	1.46	2.67	2.75	3.78	0.52		
6	0.47	0.52	0.43	0.15	0.21	0.47	0.30	0.34			1.63	1.51	1.47	3.10	3.78	3.01	2.92	2.24		
7	1.03	0.69	0.69	0.34	0.28	0.56	0.52	0.52			1.38	1.03	3.10	2.81	—	4.82	3.10	—		
8	1.55	—	0.77	0.43	0.69	0.43	0.69	0.43												
9	0.69	1.03	1.03	0.26	0.30	0.52	0.43	0.43												
10	0.77	0.52	0.69	0.04	0.13	0.09	0.19	0.26												
11	—	—	1.46	0.60	0.95	1.03	1.55	—			—	0.86	1.72	1.55	5.50	5.85	5.85	5.16		
12	—	—	0.69	0.26	0.17	0.69	0.86	—			1.72	1.03	—	—	1.03	1.72	1.03	—		
13	0.34	0.34	0.77	0.09	0.34	0.52	1.12	1.20			1.72	2.24	6.19	5.68	—	3.78	—	2.41		
14	1.38	1.20	1.89	0.52	0.52	0.52	0.86	—			2.58	1.89	4.18	5.03	4.47	4.61	4.13	3.44		
Average	1.067	0.952	1.034	0.318	0.471	0.566	0.989	0.801			1.543	1.540	3.293	3.627	3.774	3.790	3.517	2.725		
Range	1.03	0.34	0.43	0.04	0.13	0.09	0.19	0.26			0.52	0.86	1.03	1.46	1.03	1.72	1.03	0.52		
	1.72	1.69	1.89	0.60	0.95	1.03	1.55	1.52			2.58	3.10	6.19	5.68	5.51	5.85	5.85	5.16		
Total Values of Amylase Before and After Stimulation with Secretin and Mecholyl Chloride (Grams Maltose per Total Sample)																				
1	20.64	55.04	4.64	27.52	19.26	—	27.52	19.26			13.07	14.79	56.15	106.38	75.70	21.00	58.83	16.46		
2	13.42	16.86	14.44	7.87	20.64	12.38	47.82	22.05			26.78	51.07	108.13	125.80	112.15	51.26	37.79	45.41		
3	13.07	22.42	59.81	26.40	15.53	33.28	61.61	55.0			1.13	12.04	14.45	22.37	93.95	30.27	34.06	22.86		
4																				
5	5.16	11.01	65.02	4.64	5.16	17.20	51.60	11.01												
6	5.08	9.29	21.50	2.81	2.79	16.51	9.93	5.24			8.60	4.13	19.95	17.98	12.55	11.87	41.62	4.13		
7	3.10	1.12	15.77	10.15	7.74	19.91	20.64	16.51			3.61	7.22	33.56	31.99	18.65	3.01	1.46	6.71		
8	9.29	—	35.13	15.48	16.68	11.78	17.89	9.20			9.64	7.91	57.28	22.02	—	33.73	31.06	—		
9	6.88	13.42	31.99	6.19	14.15	10.81	3.87	1.50												
10	5.42	5.63	22.02	1.25	2.15	10.81	3.87	1.50												
11	—	—	64.76	13.84	12.06	14.25	5.02	10.06			—	6.88	30.96	4.64	27.53	76.05	35.10	25.31		
12	—	—	22.36	7.74	3.44	12.38	37.81	—			—	2.58	—	—	8.26	8.60	17.54	—		
13	1.38	2.34	27.53	1.89	0.54	6.19	30.19	22.38			9.16	8.95	85.69	45.41	—	11.35	—	—		
14	15.14	8.43	38.38	11.87	14.45	8.77	32.68	—			18.07	13.21	53.66	62.14	62.61	16.44	12.38	9.63		
Average	8.96	10.06	41.06	8.83	12.75	13.80	27.61	17.34			11.67	13.18	51.09	48.78	51.47	29.67	30.32	19.67		
Range	1.38	1.12	14.44	1.25	2.79	2.15	3.87	1.50			4.13	2.58	11.45	4.61	8.26	3.01	1.46	4.13		
	20.64	22.42	98.38	26.40	45.53	33.28	61.61	55.70			26.78	51.07	108.13	106.38	112.46	76.05	58.83	36.46		

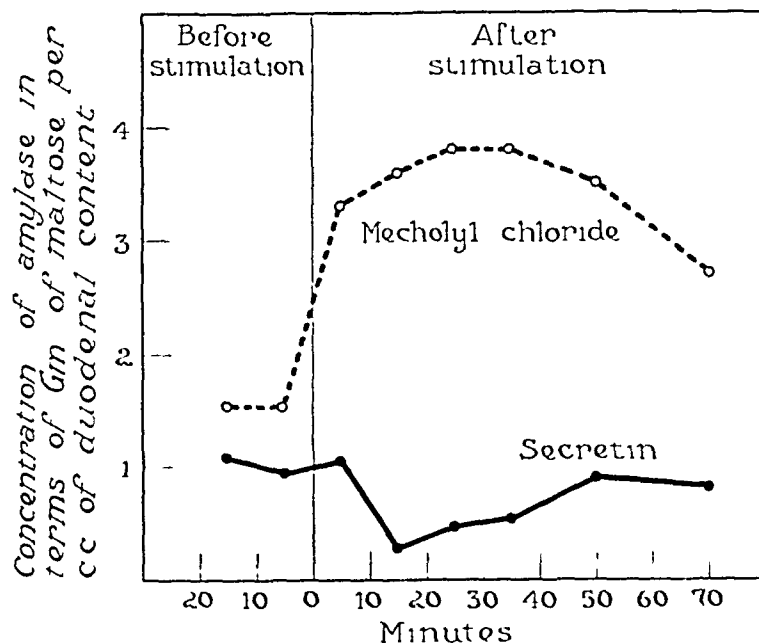


Chart 3—Average concentration of amylase per cubic centimeter of duodenal contents in a sample obtained per unit of time before and after stimulation with secretin and mecholyl chloride

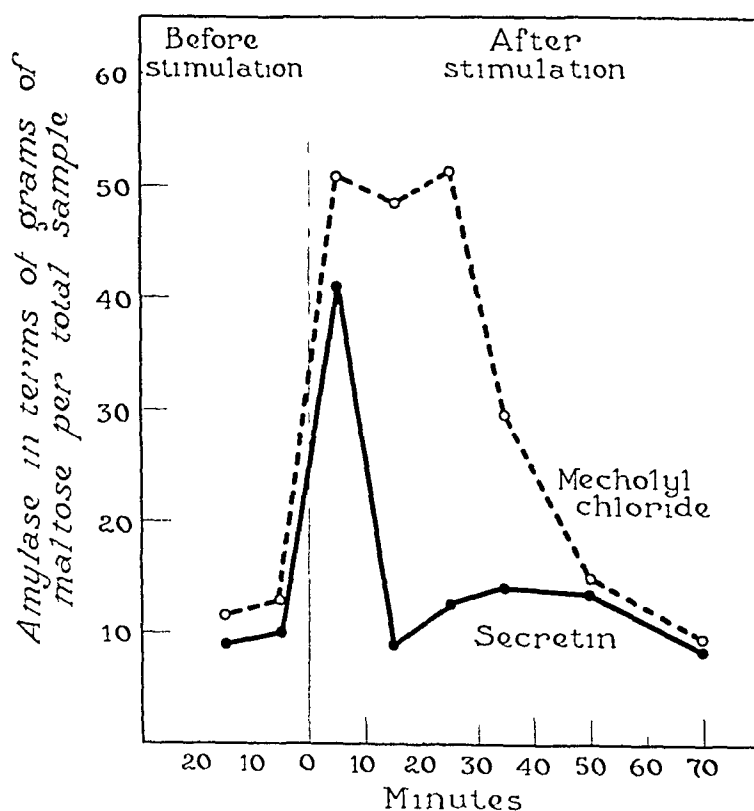


Chart 4—Average value for total amylase per total sample obtained per unit of time before and after stimulation with secretin and mecholyl chloride

TABLE 4—Concentration of Trypsin in Duodenal Content Before and After Stimulation with Secretin and Mecholyl Chloride (Cubic Centimeters of Tenth-Normal Potassium Hydroxide per Cubic Centimeter of Duodenal Juice)

Case	Before Secretin,						After Secretin						After Mecholyl Chloride					
	10 Minute Periods			20 Minute Periods			10 Minute Periods			20 Minute Periods			10 Minute Periods			20 Minute Periods		
	2	1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
1	30.0	—	57.6	3.6	—	—	18.0	9.8	15.6	24.7	27.1	80.9	53.3	16.0	40.4	28.2	—	—
2	15.6	16.8	23.5	11.2	—	—	34.2	22.4	27.3	43.5	79.5	68.6	69.8	23.9	25.6	39.4	—	—
3	16.8	24.6	43.1	33.8	47.7	60.0	61.1	59.9	12.8	14.0	12.6	16.9	67.2	6.6	25.2	19.5	—	—
4	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
5	6.0	8.0	56.7	5.4	10.5	27.5	80.0	16.0	30.0	8.3	41.6	29.8	10.8	14.3	33.0	16.0	—	—
6	10.6	20.7	50.8	13.8	11.7	37.5	36.8	11.4	37.7	7.8	24.0	22.1	8.9	1.6	1.4	4.2	—	—
7	7.8	6.4	24.0	15.5	21.8	35.6	52.0	41.8	3.7	14.1	44.1	17.2	—	17.5	25.3	—	—	—
8	—	—	45.1	30.0	11.1	20.6	24.4	11.0	11.9	14.1	—	—	—	—	—	—	—	—
9	6.0	18.2	40.3	14.4	14.1	21.0	7.2	4.0	—	—	—	—	—	—	—	—	—	—
10	11.9	13.2	118.4	17.4	14.5	10.0	10.4	46.8	—	—	—	—	—	—	—	—	—	—
11	—	4.5	66.4	17.3	21.8	26.4	9.0	—	—	—	—	—	—	—	—	—	—	—
12	—	—	35.8	27.0	18.0	19.8	57.2	—	—	—	—	—	—	—	—	—	—	—
13	5.6	11.7	59.2	4.1	15.2	9.6	29.7	28.5	5.5	6.0	35.0	20.0	—	8.0	20.4	—	—	—
14	13.2	7.0	62.4	20.7	22.4	15.3	41.8	—	—	—	—	—	—	—	—	—	—	—
Average	12.4	13.1	52.6	16.5	19.0	24.4	35.5	26.3	14.8	13.7	37.7	32.5	33.5	13.2	21.6	18.1	—	—
Range	5.6	4.5	23.5	3.6	10.5	9.2	7.2	4.0	3.7	3.8	12.6	9.9	8.9	1.6	1.4	4.2	—	—
Range	30.0	24.6	66.4	33.8	47.7	60.0	80.0	59.9	30.0	43.5	79.0	80.9	69.8	23.9	40.4	39.4	—	—

Total Trypsin of Duodenal Contents Before and After Stimulation with Secretin and Mecholyl Chloride (Cubic Centimeters of Tenth Normal Potassium Hydroxide per Total Sample)

ten minute period, reaching a level less than that noted before stimulation in 11 of the 13 cases. The concentration fell to less than 1 cc of tenth-normal potassium hydroxide in every case in the second ten minute period. The concentration of trypsin remained at less than prestimulation levels in 9 of 11 cases in the third period and in 6 of 12 in the fourth period. The concentration of trypsin in terms of cubic centimeters of tenth-normal potassium hydroxide per cubic centimeter of duodenal contents was 1 or less in every case during the third period. The lowest concentration was obtained in 9 of 13 cases in the second, in 3 of 13 in the third and in 1 of 13 in the fourth ten minute period. Although the concentration tended to remain at less than prestimulation levels, a rise greater than that in the second ten minute period usually occurred in the third and fourth periods. The concentration did not return to prestimulation levels during the course of the experiment in 10 of the 13 cases. Secretin produces a prolonged depression of the concentration of trypsin, lasting, as a rule, throughout the experiment but greatest in the second ten minute period, the depression is usually followed by a slight secondary rise which usually does not reach prestimulation levels.

Mecholyl chloride produced a contrasting effect. After stimulation with this drug (table 4), the concentration increased in every case, the increase varying from a fraction to fourfold. The concentration of trypsin, in terms of cubic centimeters of tenth-normal potassium hydroxide per cubic centimeter of duodenal content, exceeded 3 cc in 5 cases and 2.5 cc in 9 of 10 cases at some time during the poststimulation period. The maximal increase occurred three times in the first period and twice in the second, third and fourth periods, respectively. An increase occurred in the first ten minute period in 8 of 9 cases, a concentration greater than prestimulation levels was maintained in all cases in the second ten minute period, in 6 of 8 cases in the third ten minute period and in 7 of 9 cases in the fourth ten minute period. The increase persisted at greater than prestimulation levels for twenty minutes in 1 case, thirty minutes in 1 case, forty minutes in 3 cases, forty to sixty minutes in 3 cases and sixty to eighty minutes in 1 case. Mecholyl produces a prolonged rise in concentration of trypsin, in terms of cubic centimeters of tenth-normal potassium hydroxide per cubic centimeter of duodenal contents, levels greater than those before stimulation persisting sixty to eighty minutes (chart 5).

Total Amount of Trypsin—Before stimulation, the total value for trypsin per unit of time, in terms of cubic centimeters of tenth-normal potassium hydroxide per cubic centimeter of duodenal contents, varied from 3.7 to 43.5 cc and averaged 13.4 cc (table 4). After stimulation with secretin, a rapid rise in the total trypsin per unit of time occurred in all 13 cases, varying from a fraction to sixteenfold and averaging fourfold, the total value for trypsin varied between 23.5 and 66 cc during the first ten minute period. The maximal increase occurred in 12 of the 13 cases in the first period. The rapid rise in total trypsin was followed by a rapid fall in the second period in all 13, the value reaching lower than prestimulation levels in 6 of 8 cases. The fall in total trypsin was followed by a slight rise in 8 of 11 cases in the third and fourth ten minute periods. Again, it is to be emphasized that the only significant increase in the total values for trypsin occurred in the first ten minute period, when the concentration of trypsin had felt only partially the depressing effect of secretin and when the stimulating effect of secretin on volume was at its height.

After stimulation with mecholyl chloride a rise in total trypsin occurred in every case, varying from twofold to sixfold, and averaging threefold (table 4). The maximal increase occurred in 6 cases in the first, in 1 case in the second and in

2 cases in the third ten minute period, the total trypsin value returned to pre-stimulation levels in 1 case in the third, in 5 cases in the fourth ten minute period, in 1 case in the first and in 2 cases in the second twenty minute period. In 1 case the increase in total trypsin to values greater than those before stimulation persisted throughout the eighty minutes. The greatest total value for trypsin in terms of cubic centimeters of tenth-normal potassium hydroxide per ten minute period during the first four ten minute periods after stimulation with mecholyl chloride varied between 20 and 80 cc, a range of values similar to that found during the first ten minute period after stimulation with secretin. Mecholyl chloride produced a marked increase in the total values for trypsin per unit of time which persisted in general throughout the first thirty minutes, reaching prestimulation levels some time between forty and eighty minutes after stimulation, contrasting with the rapid increase in the first ten minute period following stimulation with secretin that in turn is followed by a rapid fall near prestimulation levels (chart 6)

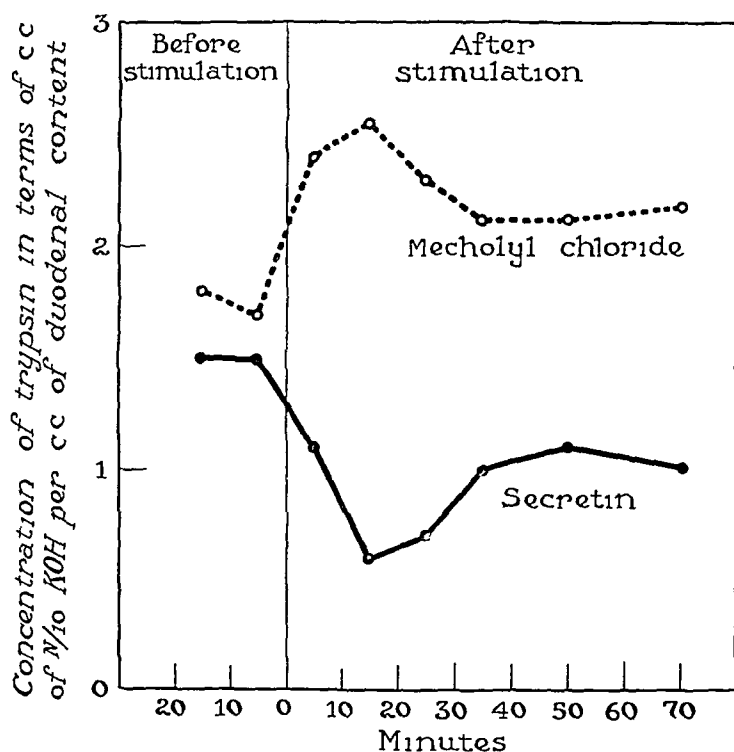


Chart 5—Average concentration of trypsin per cubic centimeter of duodenal contents in samples obtained per unit of time before and after stimulation with secretin and mecholyl chloride

Concentration of Lipase—Before stimulation, the concentration of lipase in terms of cubic centimeters of twentieth-normal sodium hydroxide per cubic centimeter of duodenal juice varied between 2 and 267 cc and averaged 76 cc (table 5). After stimulation with secretin, the concentration fell below prestimulation levels in 10 of the 13 cases during the first or second ten minute period, whereas a rise from the level of the second ten minute period occurred in 10 cases in the third ten minute period. The lowest concentration was obtained in 5 cases in the first and in 6 cases in the second ten minute period. A return to prestimulation levels occurred in 1 case in twenty minutes, in 3 cases in thirty minutes, in 1 case in forty minutes and in 1 case in eighty minutes, in 3 cases there was no return to

TABLE 5—Lipase Concentration Before and After Stimulation with Secretin and Mecholyl Chloride (Cubic Centimeters of Twentieth-Normal Sodium Hydroxide per Cubic Centimeter of Duodenal Contents)

Case	After Secretin										After Mecholyl Chloride									
	Before Secretin, 10 Minute Periods					10 Minute Periods					Before Mecholyl Chloride, 10 Minute Periods					10 Minute Periods				
	2	1	1	2	3	4	5	6			2	1	1	2	3	4	5	6		
1	1560	—	3,200	1,026	—	—	1,860	1,260			941	1,300	2,554	4,030	3,066	680	2,448	1,289		
2	3,204	1,330	930	1,058	2,904	2,568	2,760	1,182			557	1,178	1,963	1,251	1,722	532	1,217	1,216		
3	1,096	890	2,033	2,116	6,095	5,547	4,941	2,321			—	42	469	611	819	374	252	461		
4	147	664	126	18	345	50	450	1,124			—	—	—	—	—	—	—	—		
5	54	1,944	3,042	1,180	1,203	1,850	1,638	310			770	282	1,018	923	477	292	1 243	952		
6	117	712	2,275	2,920	2,903	3,730	4,360	4,180			146	626	670	836	626	104	69	258		
7	792	—	4,683	2,928	2,464	1,315	2,158	976			592	719	2,169	954	—	1,148	1,793	—		
8	940	1,365	2,728	1,944	4,465	1,869	783	490			—	—	—	—	—	—	—	—		
9	119	715	960	2,610	2,958	2,375	2,418	3,666			—	16	1,098	264	610	2,093	774	505		
10	—	560	2,848	1,811	2,294	2,236	384	—			—	12	—	—	784	620	1,904	—		
11	—	—	2,957	1,920	1,580	1,530	4,004	1 387			363	256	1,330	1,232	—	600	—	—		
12	1,060	94	6,200	572	950	888	4,841	—			630	665	1,235	1,331	1,526	1,500	420	608		
13	396	434	3,328	1,856	2,240	1,275	3,010	—			—	—	—	—	—	—	—	—		
14	862	811	3,323	1,691	2,634	2,103	2,569	1,713			—	—	—	—	—	—	—	—		
Average	54	94	126	18	345	50	384	340			146	12	670	264	662	104	69	200		
Range	3,204	1,944	4,680	2,928	6,095	5,517	4,940	4,180			941	1,390	2,554	4,030	3,066	2,093	2,418	1,289		

Lipase per Total Sample Before and After Stimulation with Secretin and Mecholyl Chloride (Cubic Centimeters of Twentieth Normal Sodium Hydroxide per Total Sample)

prestimulation levels. A glance at the figures in table 5 will show that whereas there was a tendency toward a fall after stimulation with secretin, the tendency was not nearly so marked or so precise as it was in the case of amylase or trypsin.

After stimulation with mecholyl chloride an increase in the concentration of lipase occurred in 9 of 10 cases, the increase varied from 25 to 65 per cent (table 5). The maximal concentration occurred in 1 case in the first, in 1 case in the second, in 5 cases in the fourth, in 2 cases in the fifth and in 1 case in the sixth period after stimulation. A concentration greater than that before stimulation was maintained for forty minutes in 9 of the 10, for sixty minutes in 8 of 9 and for eighty minutes in 6 of 8 subjects. In short, a prolonged rise to greater than prestimulation levels, persisting sixty to eighty minutes, occurred after stimulation with mecholyl chloride. Although this rise was not so marked as in the case of trypsin and amylase, the tendency is well seen and is in contrast with the behavior of concentration of lipase after stimulation with secretin (chart 7).

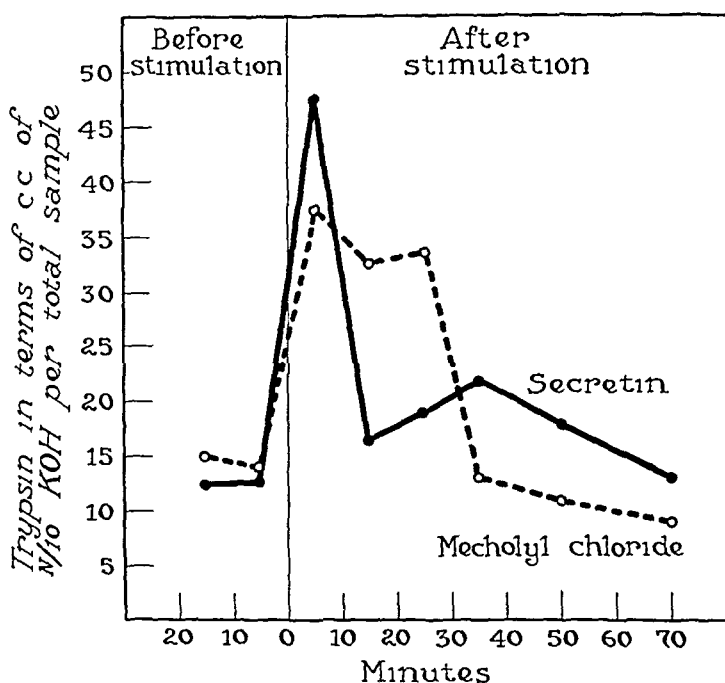


Chart 6—Average value for total trypsin per total sample obtained per unit of time before and after stimulation with secretin and mecholyl chloride

Lipase per Total Sample—Before stimulation, the total value for lipase in the duodenal contents collected in a ten minute period, in terms of cubic centimeters of twentieth-normal sodium hydroxide, varied from 12 to 3,200 cc and averaged 700 cc (table 5). After stimulation with secretin, the lipase per total sample increased rapidly in 11 of 13 cases, varied from one-half to thirtyfold in the 11 cases and averaged three and a half times the prestimulation value. A slight decrease occurred in 2 of the 13 cases. The greatest increase occurred when prestimulation levels were low. The maximal increase occurred in the first ten minute period in 7 cases, in the third ten minute period in 2 cases and in the fourth ten minute period in 2 cases, a fall occurred in the second ten minute period in 8 and was followed by a secondary rise in only 3 of the 8 cases. The total amount returned to prestimulation levels in 2 cases in the fourth ten minute period, in 3

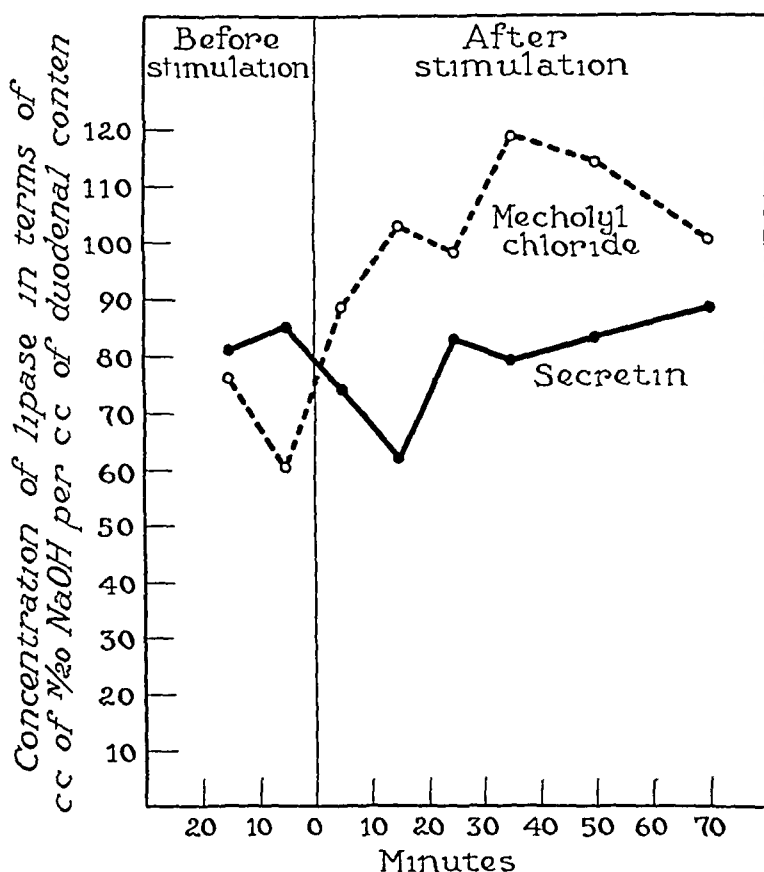


Chart 7—Average concentration of lipase per cubic centimeter of duodenal contents in the sample obtained per unit of time before and after stimulation with secretin and mecholyl chloride

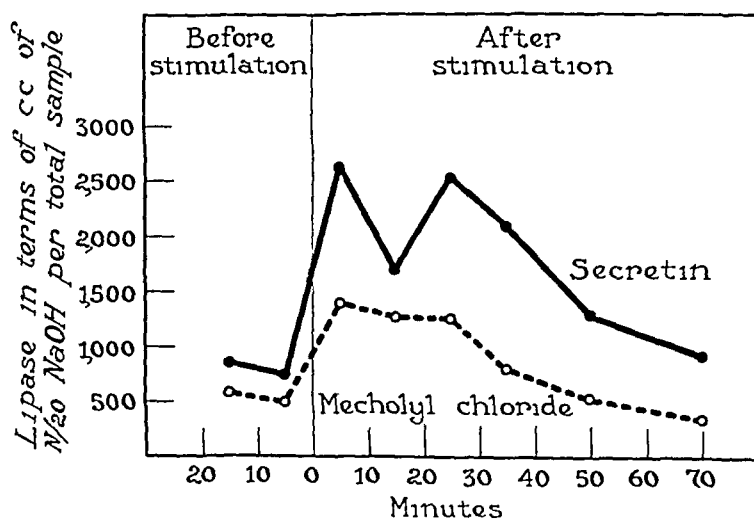


Chart 8—Average value for total lipase per sample obtained during the unit of time before and after stimulation with secretin and mecholyl chloride

cases in the first twenty minute period and in 2 cases in the second twenty minute period but persisted above prestimulation levels in 4 cases during the course of the experiment. In 12 of 13 cases a figure of more than 2,500 cc was reached at some time during the period after stimulation. Secretin produces a rapid increase in the total value for lipase, the maximal increase usually occurring in the first ten minute period. The increase is much more prolonged than in the case of amylase and trypsin. The total value returns to prestimulation levels in the forty to eighty minute period, or later.

After stimulation with mecholyl chloride an increase in the total value for lipase per unit of time in terms of twentieth-normal sodium hydroxide occurred in all 10 cases, varying from one-half to one hundred and fifty times the original value, depending to a considerable extent on the presecretory levels, the maximal increase occurred in the first ten minute period in 5 cases, in the second ten minute period in 2 and in the third ten minute period in 3 (table 5). The total value for lipase returned to prestimulation levels in 1 case in the third and in 4 in the fourth ten minute period but persisted beyond forty minutes in half of the subjects,¹⁴ returning to prestimulation levels in 2 cases in forty to sixty minute intervals but persisting beyond eighty minutes in 3 cases. It is to be noted that in all these 3 cases the prestimulation levels were very low. Mecholyl chloride produces a marked increase in the total value for lipase, averaging two and a half times the original value, that persists throughout the first three ten minute periods, reaching prestimulation levels in the thirty to forty minute or forty to sixty minute period (chart 8).

SUMMARY AND CONCLUSIONS

Continuous suction through a double tube has been used in the study of pancreatic secretion in man after stimulation with (1) secretin and (2) mecholyl chloride. The tube was composed of two lumens. When in correct position, one lumen opened into the stomach for removal of gastric contents and for prevention of entrance of gastric contents into the duodenum, the other lumen opened into the duodenal cavity for the removal of duodenal contents. The method has proved mechanically satisfactory for this purpose.

Secretin and mecholyl chloride produced contrasting effects on pancreatic secretion. Secretin produced a large volume of duodenal contents, increased the p_H values and effected a prolonged reduction in the concentration of enzymes. Mecholyl chloride, on the other hand, increased the volume of duodenal contents only slightly, did not appreciably affect the p_H values and provoked a prolonged increase in the concentration of enzymes.

Although the total value for the several enzymes per unit of time was increased by both secretin and mecholyl chloride, the increase in the total value for amylase and trypsin following stimulation with secretin occurred almost entirely during the first ten minute period after stimulation but was prolonged for thirty minutes or longer after stimulation with mecholyl chloride. The increase in total value for these enzymes appeared to be due to a washing-out process in the case

of secretin but was due to an active secretion of enzymes in the case of mecholyl chloride. The total value for lipase was likewise increased after each type of stimulant was given, but the increase was more prolonged after stimulation with secretin than were the total values for amylase and trypsin. The significance of this different type of behavior is not clear.

Stimulation with secretin demonstrated that the pancreas is capable of secreting a large volume of highly alkaline juice. Even the increase in total value for the enzymes secreted during the first ten minute period after stimulation was more of a measure of capacity of the pancreas to secrete a large volume of pancreatic juice than of its capacity for secreting enzymes. Stimulation with mecholyl chloride, on the other hand, demonstrated that the pancreas is able to secrete a juice rich in enzymes. As in animals, the humoral mechanism in man produces an effect on pancreatic secretion which differs from that produced by the vagal mechanism.

The effects of secretin and mecholyl chloride on pancreatic secretion follow a definite pattern, they vary, however, in magnitude from one experiment to another but to a lesser degree when multiple tests are performed on the same subject. After stimulation with secretin, the concentration of amylase in terms of grams of maltose per cubic centimeter of duodenal contents fell usually below 0.5 Gm. of maltose, and the concentration of trypsin in terms of twentieth-normal potassium hydroxide per cubic centimeter of duodenal contents, to less than 1 cc. After stimulation with mecholyl chloride, the concentration of amylase usually reached 3.7 Gm., and that of trypsin, 2.5 cc.

After stimulation with secretin, the total value for the first ten minute period in the case of amylase varied from 10 to 100 Gm., and in the case of trypsin, from 20 to 70 cc., the value for lipase during the same period varied from 100 to 6,000 cc., as measured in terms of twentieth-normal sodium hydroxide. After stimulation with mecholyl chloride, the highest total values per unit of time following stimulation varied from 14 to 125 Gm. of maltose per ten minute period in the case of amylase, from 10 to 80 cc. of tenth-normal potassium hydroxide per ten minute period in the case of trypsin and from 1,100 to 4,000 cc. of twentieth-normal sodium hydroxide per ten minute period in the case of lipase. The fluctuations in total values per unit of time result from both the variations in the volume of duodenal contents obtained and the variations in the concentration of enzymes and occur at least in part because of the mechanical difficulties inherent in the quantitative removal of the duodenal contents.

Both concentrations and total values for enzymes should be used in determining pancreatic function. However, because the variations in the

total values for normal persons after stimulation with both secretin and mecholyl chloride have proved to be greater than the variations in the concentrations after stimulation with mecholyl chloride, the concentrations after stimulation with mecholyl chloride may prove to be a more reliable index of pancreatic function than the total values per unit of time after stimulation with either secretin or mecholyl chloride

The proper exploration of pancreatic function demands investigation of both the humoral and the vagal mechanism of control of pancreatic function

Progress in Internal Medicine

VASCULAR DISEASES

A REVIEW OF SOME OF THE RECENT LITERATURE, WITH A
CRITICAL REVIEW OF THE SURGICAL TREATMENT

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CHICAGO

REVIEW OF SOME OF THE RECENT LITERATURE

BY DR VAN DELLEN AND DR SCUPHAM

In these reviews of the past six years we have not attempted to include all of the available literature on vascular diseases. Many deserving articles have undoubtedly been missed, and consequently the reviews must not be considered complete. Preference was usually given to articles containing original ideas, as well as to those confirming or disproving existing beliefs. Many articles were included on merit alone, or their contents were thought worthy of repetition. The study of vascular diseases is not without its difficulties and is open to criticism. The vast amount of instrumentation is certainly unnecessary for diagnosis, in the majority of cases the history and findings alone are sufficient. Arteriosclerosis, the most prevalent vascular disease, has received too little attention.

Three monographs dealing with diseases of the peripheral vessels were published during the past year. Of the three, Homans' ¹ is probably the most complete, with ample discussion on disorders of the arteries, veins and lymphatics. Conservative and radical forms of therapy are adequately outlined, with numerous illustrations of important aids in diagnosis and treatment. Although certain established procedures are

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1 Homans, J. Circulatory Diseases of the Extremities, New York, The Macmillan Company, 1939

not included, one is not wanting in sufficient armamentarium to treat adequately the majority of patients. In the monograph by Ochsner and Mahorner² the bulk of material is devoted to venous disorders. These authors covered the subject of varicose veins in a concise and authoritative manner, with the help of excellent diagrams and photographs. The history of the treatment of varicose veins is included, as well as a review of the anatomy, pathology, physiology, etiology, clinical aspects, examination and treatment. Collens and Wilensky³ more closely adhered to the subject of peripheral arterial disturbances. Many necessary surgical procedures, as well as congenital anomalies, aneurysms and varicose veins, are not discussed. Too much detail is allotted to certain tests and apparatus of the authors, while others equally as important are less favorably treated.

Saland and his colleagues⁴ suggested criteria for the classification and diagnosis of peripheral vascular diseases, based on the diagnostic criteria for heart disease published by the Heart Committee of the New York Tuberculosis and Health Association. No claim was made by the authors that these represented ultimate and immutable principles. This was wise, as many of the statements are open to question. It was suggested that a comprehensive diagnosis of peripheral vascular disease should include a statement of (a) the etiologic agent or agents, (b) the anatomic status, (c) the extent of physiologic impairment and (d) the functional capacity of the patient. The names of all the diseases are listed under the etiologic agent or agents, with the criteria for diagnosis in each case. To reach an anatomic diagnosis one uses tests to ascertain whether the vessel is organically or functionally closed and the effect of such closure on the surrounding tissues. The physiologic changes refer mainly to the symptoms, amount of spasm and vascular reserve, which again reverts to the amount of spasm and the capacity for dilatation. The functional diagnosis is similar to that of heart disease. Such a classification is desirable and is a step in the right direction. It is, however, difficult of application because, in the present state of knowledge, the etiologic factors in many vascular disorders are uncertain. The disorders themselves are syndromes rather than disease entities. As an example, erythromelalgia occurs as a symptom of several diseases, including arteriosclerosis and polycythaemia vera.

2 Ochsner, A., and Mahorner, H. *Varicose Veins*, St. Louis, C. V. Mosby Company, 1939.

3 Collens, W. S., and Wilensky, N. D. *Peripheral Vascular Diseases: Diagnosis and Treatment*, Springfield, Ill., Charles C. Thomas, Publisher, 1939.

4 Saland, G., Klem, C., Zurrow, H., Gootnick, A., and Katz, A. Criteria for the Classification and Diagnosis of Peripheral Vascular Diseases, *Arch. Int. Med.* 65: 1035 (May) 1940.

PHYSIOLOGY

Roth, Horton and Sheard⁵ continued their studies on the role of the extremities in the dissipation of heat. Data were obtained from 2 normal subjects. It was shown that relative humidity had little effect on the cutaneous temperatures of the body, as indicated by changes in the temperature of the fingers and toes. Studies were made when the body was subjected to fixed environmental temperatures ranging from approximately 23 to 28 C (73.4 to 82.4 F), with a fairly wide range (35 to 75 per cent) of relative humidity. They expressed the opinion that minor increases in cutaneous temperature which might be produced by large increases in atmospheric humidity were overshadowed by the relatively large thermal changes in the extremities due to small changes in environmental temperatures. They concluded that under these conditions the dissipation of heat from the body is dependent chiefly on the environmental temperature and is little influenced by relative humidity. Sheard, Horton and Williams⁶ studied the rates of cooling and warming under normal circulatory conditions and in peripheral vascular diseases. The data obtained from a group of normal persons were subjected to mathematical analysis. They found the rate of cooling, in each instance, to be rather constant, ranging from 0.02 to 0.05 C (0.36 to 0.09 F) per minute. Patients with peripheral vascular disease gave a similar response. This is logical since, if account is taken of the metabolic rates, the rates of cooling of the toes are the same under normal circulatory conditions and in peripheral vascular disease, vasoconstriction, whether spastic or obstructive, being operative in both.

In contrast, the rate of warming was found to differ in normal and in pathologic states. In normal persons two distinct rates were noted. The initial rates were found to be between 0.015 and 0.03 C (0.027 and 0.054 F) per minute and were constant until the temperature of the toes reached a value of 27 to 28 C (80.6 to 82.4 F). At this stage the rate became faster, lying between 0.04 and 0.10 C (0.072 and 0.18 F) per minute. The initial rate was considered to represent only the rate of environmental heating of the tissue, whereas the second rate showed the combined effects of the heating of tissue by the environment and the increased supply of blood brought to the tissue. In cases in which abnormal vasoconstriction or organic occlusion was present the initial rate of heating was found to be similar to that of normal persons.

5 Roth, G. M., Horton, B. T., and Sheard, C. The Relative Roles of the Extremities in the Dissipation of Heat from the Human Body Under Various Environmental Temperatures and Relative Humidities, *Am J Physiol* **128**: 782 (March) 1940.

6 Sheard, C., Horton, B. T., and Williams, M. M. D. Rates of Cooling and Warming of the Extremities in Normal Circulatory Conditions and in Peripheral Vascular Diseases, *Proc Staff Meet, Mayo Clin* **14**: 541 (Aug 23) 1939.

On the other hand, in the range of environmental temperatures in which vasodilatation occurred normally, there were abnormally low or definitely decreased rates of warming. In many cases of essential hypertension similar responses were given, showing a considerable degree of vasoconstriction. In cases of thromboangitis obliterans the initial rate of warming generally was near the lowest limit for normal circulation, namely, 0.015 C (0.027 F) per minute. In some instances a slight increase took place after the temperature of the toes reached values of from 29 to 30 C (84.2 to 86 F), but in many the rate decreased after this level had been reached.

Nielsen, Herrington and Winslow⁷ studied the effect on the peripheral circulation of a passive change in body posture in persons subjected to high environmental temperatures. Observations were made on patients lying on a tilting table at room temperatures of 30 and 35.6 C (86 and 96.1 F). After the change in posture from the horizontal to the "feet-down" position (45 degrees from horizontal), the rectal and toe temperatures were increased and the peripheral cutaneous temperature was decreased. The peripheral constriction increased with progressively higher environmental temperatures and higher angles of tilting. A tendency to collapse was not uncommon when both the environmental temperatures and the angles of tilting were greatly increased. The rise in rectal temperature was roughly proportional to the degree of vasoconstriction in the extremities. This was thought to be functionally associated with the stimulus to increased evaporation resulting from disturbance in heat regulation when peripheral vasoconstriction took place. The authors expressed the opinion that the vasoconstriction in the skin with the patient in the vertical position was related to the effect of gravity on the circulation, particularly in persons with decreased venous return and cardiac output. This appeared as a logical assumption, as Asmussen, Christensen and Nielsen⁸ had previously shown that the decrease in cardiac output was compensated by vasoconstriction in such organs as the intestines and kidneys.

Blood Flow—Wright and Phelps⁹ stated that in spite of the many advantages of the plethysmographic method of Hewlett and Van Zwaluwenburg for determining blood flow in the limbs, and even more of its modification by subsequent workers, it has a number of hidden

7 Nielsen, M., Herrington, L. P., and Winslow, C.-E. The Effect of Posture upon Peripheral Circulation, *Am J Physiol* **127**: 573 (Oct.) 1939.

8 Asmussen, E., Christensen, E. H., and Nielsen, M. Ueber die Kreislauffuffizienz in stehender Stellung bei normalem arteriellen Druck und herabgesetztem Minutenvolumen, *Skandinav Arch f Physiol* **81**: 214, 1939.

9 Wright, G. W., and Phelps, K. A Comparison of Procedures for Increasing Blood Flow to Limbs Using an Improved Optical Plethysmograph, *J Clin Investigation* **19**: 273 (March) 1940.

faults which lead to inaccuracies in the estimation of flow under various conditions. Among these are the yielding diaphragm surrounding the limb and closing the plethysmograph, displacement of fluid into the plethysmograph by inflation of the collecting cuff and lack of sensitivity of the entire apparatus.

The authors then described a boot plethysmograph which is easy to apply and calibrate, the open end of which is sealed around the leg without constriction by the use of plaster of paris and hard paste of zinc oxide, and which is comfortable for prolonged periods of study. The apparatus is connected with a Frank segment capsule, giving the entire system frequencies up to 100 per second.

To obviate the artefacts incurred through displacement of fluid into the plethysmograph by the inflated cuff, an arrangement of stopcocks is provided by which the collecting cuff is inflated while the plethysmograph and recording capsule remain open to the atmosphere, but exactly one second later the system is automatically closed and the changes in volume are recorded. The use of a full pulse beat starting exactly one and six-tenths seconds after inflation is used to measure the net flow per cycle. From this, volume flow per minute per hundred cubic centimeters of leg substance is calculated in the conventional manner.

The phasic arterial blood flow of the leg recorded in this way for normal subjects at rest in a warm room (28 to 30 C [82.4 to 86 F]) showed three distinct variations during each cycle: (1) a rapid systolic forward flow, (2) a slower, smaller and variable systolic backflow, and (3) a slow forward diastolic flow. The net arterial inflow depends not only on phase 1 plus phase 3 but also on the amount subtracted from phase 2. All of these varied under different circumstances. Since only the amplitude (phase 1) of the pulse volume is recorded by plethysmographs or oscillometers, these methods give no quantitative estimate of changes in volume flow, and under some conditions they do not show even the correct directional changes.

The resting flow determined by the procedure described by the authors remained constant within approximately 6 per cent of the mean during repeated determinations within an hour. It varied greatly in different persons or in the same person from day to day unless strictly basal conditions were observed.

A study of various procedures suggested for promoting a maximal blood flow in the leg showed that direct application of heat and sciatic nerve block were the most efficacious. Application of heat to both upper extremities (reflex heat) produced an effect only about one half as great. Wright and Phelps were unable to detect any increase in blood flow after effective spinal anesthesia or sacral diathermy.

Other procedures which affected the heart rate or blood pressure significantly influenced blood flow in a variable manner. Amyl nitrite,

for example, increased the amplitude of oscillations, but often caused an actual decrease in volume flow

Burton¹⁰ studied the momentary fluctuations in the blood flow to the fingers. He used a simple finger plethysmograph adapted to measure volume pulsations at six second intervals. He found these fluctuations to be rhythmic and to consist of two main components, namely a respiratory fluctuation of small amplitude and a periodic constriction of slower rhythm and large amplitude. These were noted to be simultaneous in all digits and were accompanied by cardiac acceleration and rise of blood pressure, indicating activity of the entire peripheral sympathetic system.

Burton also noted that the rhythm was modified by factors in temperature regulation. The amplitude of the waves was greatest at the middle ranges of rates of blood flow and at lower temperatures, being less during dilatation and least during constriction. The frequency of the rhythm was also modified by the same factors, being greatest with cooler temperatures and lower values for rate of blood flow.

Burton expressed the opinion that the tremendous range of rates of blood flow is made possible by the arteriovenous anastomoses and represents not a metabolic need but a purely mechanical means of assisting regulation of temperature by elimination of body heat. This is accomplished, therefore, not by allowing the peripheral blood flow to assume an appropriate steady level but by the adjustment of an average flow which fluctuates rhythmically between high and low values.

Mann, Herrick, Essex and Baldes¹¹ studied the flow of blood in vessels in which the lumen was mechanically constricted. These studies were made on the carotid artery of dogs, the constricting units being less than 1 cm. in length. The lumen had to be constricted to a considerable degree before the blood flow was significantly reduced. The results were expressed in terms of the reduction in external diameter, internal diameter and area of the lumen. The external diameter could be reduced 40 per cent without any significant reduction in blood flow, but when it was reduced as much as 60 per cent the blood flow decreased 49 per cent. On the other hand, the internal diameter could be reduced 70 per cent before a 50 per cent reduction in blood flow took place. When stated in terms of the area of the lumen the results were more striking. The area of the lumen could be reduced 50 per cent without any change in blood flow, and could be reduced as much as 90 per cent before a 50 per cent reduction in blood flow occurred.

10 Burton, A. C. The Range and Variability of the Blood Flow in the Human Fingers and the Vasomotor Regulation of the Body Temperature, *Am. J. Physiol.* **127**: 437 (Oct.) 1939.

11 Mann, F. C., Herrick, J. F., Essex, H. E., and Baldes, E. J. Effect on Blood Flow of Decreasing Lumen of Blood Vessel, *Surgery* **4**: 249 (Aug.) 1938.

Circulation Time—Kvale and Allen¹² studied in greater detail the solution introduced by Spier, Wright and Saylor for study of the circulation time. This fluid consists of a physiologic solution of sodium chloride containing calcium gluconate and magnesium and cupric sulfate. The circulation was timed by the occurrence of a warm sensation in the tongue, perineum, hands and feet following the intravenous injection of the solution. A "blank" was recorded when no sensation was felt in one area or another. The use of this solution was found to be a safe and good method, as it fulfilled the usual qualifications for fluids of this type. The authors, however, were unable to show any evidence that the sensation of warmth produced in the throat, hands, perineum and feet indicated that the fluid had arrived in these areas. They agreed that a reaction time must occur, which may be variable, thus influencing the results, and that consequently the figures obtained were valid only for comparative purposes.

Average values were obtained on normal subjects under controlled conditions. The ranges in time increased, being least in the "arm to tongue" time and greatest in the "arm to foot" time. Wide ranges in time demonstrated that the speed of blood flow varies widely in the same person under different conditions, but that under similar and basal conditions the velocity of flow is remarkably constant.

In cases of thromboangitis obliterans and arteriosclerosis obliterans the speed of blood flow to the hands and feet was usually diminished, depending on the degree of vascular obliteration. Inconsistency of results led the authors to conclude that this test for circulation time could not be used in diagnosis of occlusive arterial disease. In cases of hyperthyroidism the speed of flow of blood was increased in the arteries as well as in the veins.

"Ventricle to perineum" circulation time was calculated by subtracting the "arm to tongue" time from the "arm to perineum" time. Similarly, the "arm to hand" time minus the "arm to tongue" time equaled the "ventricle to hand" time, and the "arm to foot" time minus the "arm to tongue" time, the "ventricle to foot" time. Although these "times" were assumed, they furnished the first means of calculating the velocity of arterial blood flow in man.

Berk¹³ made similar observations on circulation time, using 5 cc of a 10 per cent solution of magnesium sulfate. Circulation times were determined on 200 normal persons and on 21 patients with peripheral vascular diseases. Berk studied the "arm to hand" and the "arm to

12 Kvale, W. F., and Allen, E. V. The Rate of the Circulation in the Arteries and Veins of Man. I. Studies of Normal Subjects and Those with Occlusive Arterial Disease and Hyperthyroidism, *Am Heart J* **18** 519 (Nov) 1939.

13 Berk, J. E. Circulation Time (Magnesium Sulfate Method) in the Diagnosis of Peripheral Vascular Disease, *Am J M Sc* **199** 505 (April) 1940.

foot" time His figures were considerably higher than those obtained by Kvale and Allen, as well as other authors, in this type of test As in the previous article, the readings for patients with peripheral vascular diseases exhibited a tendency toward a longer circulation time, as well as an increase in the number of "blanks"

Kvale and Allen¹⁴ also studied the influence of various physiologic factors on the circulation time, using the same method During digestion the speed of blood flow was found to be increased The speed of circulation to the feet was decreased when a patient stood erect This was thought to be due to vasoconstriction which occurred on standing Exercise increased the speed of circulation Marked rises in pulse rate, without affecting the blood pressure significantly, and with little or no effect on the temperature of the skin, increased the velocity of blood flow Minor variations in pulse rate had no effect on the velocity of flow The authors also noted that the velocity of the flow of blood in the peripheral arteries of man dependent on the cutaneous temperature Increasing the temperature increased the speed of flow, and decreasing the temperature decreased the speed of flow The latter findings are in accord with those of Stead and Kunkel,¹⁵ who showed that the blood flow of an extremity varied with changes in the local temperature of that extremity In 6 subjects the "elbow to carotid sinus" circulation time was measured by means of injection of a solution of sodium cyanide in each arm The two upper extremities were kept at different temperatures by immersing one hand in water at 23 to 30 C and the other in water at 40 to 43 C The circulation time in the cool arm averaged thirty-two and three-tenths seconds and that in the warm arm eighteen and five-tenths seconds Incidentally, these circulation times for sodium cyanide were slower than those of Kvale and Allen¹⁶ for similar distances The latter authors made note of this in comparing the two methods By mixing a solution of sodium cyanide with the solution they used and injecting this mixture into the cubital vein, they showed that there was an error in the sodium cyanide method The time required for blood to flow from an arm vein to the carotid sinus as ascertained by injection of a solution of sodium cyanide, appeared to be about three seconds more than the time actually required for blood to flow from an arm vein to the tongue

14 Kvale, W F, and Allen, E V The Rate of the Circulation in the Arteries and Veins of Man III The Influence of Temperature of the Skin, Digestion, Posture and Exercise, *Am Heart J* **18** 546 (Nov) 1939

15 Stead, E A, Jr, and Kunkel, P Influence of the Peripheral Circulation in the Upper Extremity on the Circulation Time as Measured by the Sodium Cyanide Method, *Am J M Sc* **198** 49 (July) 1939

16 Kvale, W F, and Allen, E V The Rate of the Circulation in the Arteries and Veins of Man IV An Error in the Sodium Cyanide Method of Determining Speed of Venous Blood Flow, *Am Heart J* **18** 557 (Nov) 1939

In a later publication, Kvale, Smith and Allen¹⁷ reviewed all the foregoing material. In addition, they showed that the speed of flow of blood after an operation is usually reduced in the veins of the lower extremities. In the "arm to tongue" circulation time the decrease was noted after the first forty-eight hours, but the time then increased until the thirteenth postoperative day.

Velocity of Pulse Wave—Matthes, Gross and Goepfert¹⁸ studied the pulse wave in the arteries of the upper extremity. The speed of the pulse wave in most of the arteries (wrist to tip of finger) was considerably lower than that in the medium arteries (cubital to radial region). The authors thus assumed an air chamber action of the most peripheral arteries. They concluded that the peripheral volume pulse is a fluctuation of the blood content of the small and smallest arteries of the skin, as capillaries and venules do not pulsate. Variations in the blood content of these vessels were found to occur especially in arrhythmias of the heart, making characteristic patterns.

Capillaries—Clark and Clark¹⁹ observed the growth of blood capillaries in the adult rabbit. Microscopic studies in which the finest details were observed with great clearness demonstrated that new blood vessels arise by a process of capillary sprouting from preexisting vascular endothelium and that the endothelium of the growing vessels remains specific. The authors showed that the regenerating capillaries of the rabbit resembled in their manner of growth, through anastomoses with neighboring vessels and lumen formation, the growing capillaries of the amphibian larvae.

Cells resembling fibroblasts were observed to adhere to the walls of newly formed capillaries, remaining as adventitial cells. The tissue outside growing capillaries in the transparent chamber underwent characteristic changes as the new vessels advanced and received a blood supply. Fibrin dissolved, and the extravascular fluid changed to a tissue substance resembling a soft gel. Subsequently the fibroblasts migrated into the growth space, and connective tissue fibers formed between the new capillaries.

Capillary growth occurred rapidly and was most abundant in the presence of an active circulation and an inflammatory exudate. It became slower and sometimes ceased in the chamber areas which became stable and were protected from movement and irritation, even in the

17 Kvale, W. F., Smith, L. A., and Allen, E. V. Speed of Blood Flow in the Arteries and in the Veins of Man, *Arch. Surg.* **40**: 344 (Feb.) 1940.

18 Matthes, K., Gross, F., and Goepfert, H. Untersuchungen über die Form des peripheren Pulses beim Menschen, *Arch. f. d. ges. Physiol.* **242**: 437, 1939.

19 Clark, E. R., and Clark, E. L. Microscopic Observations on Growth of Blood Capillaries in Living Mammal, *Am. J. Anat.* **64**: 251 (March) 1939.

presence of sufficient space for further extension. The same growth conditions which favored the formation of new blood vessels also stimulated the growth of other tissues in the same region.

The character of the cutaneous capillary structure of 1,100 schizophrenic patients was studied by Olkon²⁰ and compared with that of normal persons. In cases of schizophrenia the cutaneous capillaries showed striking deviations, consisting of reduction in number, few comma shapes, a paler color, lack of uniformity in size and a variety of bizarre shapes—spiral, crescent, hairpin-like and stellate forms and dilated, ameboid forms with pseudopodia. Moreover, the flow through the capillaries was seldom uniform, at times it was more rapid and at times slower than normal, at other times the contractions and dilations were remarkably irregular. Another striking feature was the frequent occurrence of capillary hemorrhage among excited schizophrenic patients. In cases of hebephrenia of long standing, sparseness of capillaries was the most marked feature, aside from the bizarre shapes already mentioned. Schizophrenic patients showed these changes, whereas normal persons of similar age did not. From these observations the author expressed the belief that since in organic and vegetative derangements there are definite disturbances in the capillaries, their presence in these patients may be corroborative evidence of the increasingly accepted theory that schizophrenia is a vegetative and metabolic disorder.

Eichna and Bordley²¹ reviewed studies on capillary blood pressure and concluded that the direct microinjection method of Landis was more accurate than the indirect pressure capsule method of Danzer and Hooker. Comparisons were made at normal and at elevated levels of venous pressure. A critical test was used to evaluate the reliability of the two methods. In this test a pneumatic cuff, encircling the upper portion of the arm, was inflated to pressures below diastolic arterial pressure. The venous pressure in the hand rose to and above the cuff pressure. The extent of this rise was found to be influenced by the difference between the level in the cuff and that in the hand. The capillary blood pressure in the nail fold, recorded by the direct method, was found always to exceed the venous pressure in the hand. This phenomenon could not be demonstrated with the indirect method, as no correlation between capillary and cuff pressure was obtained. The authors thus concluded that of the two methods the direct one afforded an accurate measurement of the capillary blood pressure.

20 Olkon, D. M. Capillary Structure in Patients with Schizophrenia, *Arch Neurol & Psychiat* **42** 652 (Oct) 1939.

21 Eichna, L. W., and Bordley, J., III. Capillary Blood Pressure in Man. Comparison of Direct and Indirect Methods of Measurement, *J Clin Investigation* **18** 695 (Nov) 1939.

In 26 of 145 patients, apparently free from circulatory disorders, Naumann²² found the pressure in the dorsalis pedis artery to be lower than that in the radial artery. In all the other patients the reverse was observed to be true.

Oscillometry—Atlas²³ found the practical application of the oscillometer to be disappointing because of the confusing results often obtained. Readings differed with the same person at morning and at night. Slender persons gave different readings than robust ones. On the premise that peripheral arteriosclerosis involves the lower extremities to a much greater extent than it does the upper, oscillometric readings at any given level in the lower extremities should, as the disease progresses, decrease proportionately more than those at any given level in the upper extremities. Oscillometric readings were thus taken at a given level in both the upper and the lower extremities. With the reading obtained at the supramalleolar level as the numerator and that at the distal third of the forearm as the denominator, a ratio was established which in 86 patients free from vascular diseases was found to be between 1 and 2. In no case was the ratio less than 1. In a group of 30 ambulatory patients with signs and symptoms of peripheral arteriosclerosis this ratio was found to be less than 1. In none of the latter group could pulsations be felt. This test will thus enable the examiner to demonstrate in a roughly quantitative way decreased arterial pulsations in the lower part of the leg.

Arteriography—Dimitza and Jaeger²⁴ listed the usual indications for arteriography, including its usefulness in visualizing the vessels prior to amputation and in determining the degree of collateral circulation. The authors also employed this method of vascular study to differentiate organic lesions from merely vasoneurotic symptom complexes when the symptoms were doubtful. Of particular value was its use in post-traumatic circulatory disturbances, especially when there was a question of malingering. In some cases the injection of the contrast medium had a definite therapeutic effect, an observation which had previously been noted. In 7 cases (a total of 70) the material was injected periarterially, but no untoward effects were noted, other than nausea in 1 and fever in 2 cases.

Tissue Pressure—Mayerson and Burch²⁵ studied the effect of posture on venous and tissue pressures in patients subject to syncope.

22 Naumann, M. Der Blutdruck in der Arteria dorsalis pedis in der Norm und bei Kreislaufstörungen, *Ztschr f Kreislaufforsch* **31** 513 (July 15) 1939.

23 Atlas, L. N. Oscillometry in Diagnosis of Arteriosclerosis of the Lower Extremities, *Arch Int Med* **63** 1158 (June) 1939.

24 Dimitza, A., and Jaeger, W. Ueber die Indikation der Arteriographie, *Fortschr a d Geb d Rontgenstrahlen* **58** 40 (July) 1938.

25 Mayerson, H. S., and Burch, G. E. Relationships of Tissue (Subcutaneous and Intramuscular) and Venous Pressures to Syncope Induced in Man by Gravity, *Am J Physiol* **128** 258 (Jan) 1940.

on changes in position. They found that the venous (foot) and intramuscular (gastrocnemius) pressures in the resting horizontal position were lower in persons who were liable to postural syncope than in those who were not. Tilting the subjects from the horizontal to the upright (75 degree) position was followed by immediate and simultaneous rises in venous, subcutaneous and intramuscular pressures. Subjects who did not have syncope showed a secondary, usually more marked, increase in intramuscular pressure during the upright period, a change which was absent in those who showed circulatory embarrassment. Intramuscular pressure was affected by the tonus of the muscle fibers, as well as by the amount of intravascular and extravascular fluid present. When the tonus was low the value for intramuscular pressure tended to approach that for subcutaneous pressure.

Effect of Drugs—During the past few years articles have appeared demonstrating differences between the vessels of the skin and those of deeper structures. The responses of these types of vessels to various therapeutic procedures were in many cases not necessarily parallel. Such differences were demonstrated by Friedlander, Bierman and Silbert,²⁶ who recorded the changes in temperature in the muscles of the calf and in the skin of the feet following the intravenous administration of typhoid vaccine. The temperatures employed ranged from 99 to 101 F, those frequently used therapeutically. Within from sixty to ninety minutes after the injection, both the rectal and the cutaneous temperature increased, but a gradual fall in the temperature of the calf muscle was noted. In many of the cases the cutaneous temperature dropped at the onset of the chill but rose above the initial level after the tremors subsided. Muscle temperature was not affected by either chills or tremors. The authors concluded from their data that an elevation of systemic temperature to 101 F is associated with an increase in the circulation of the skin of the feet and a decrease in the circulation of the calf muscles. They expressed the belief that this type of therapy might be beneficial for ulcers, but that its use for relief of intermittent claudication appeared to have no physiologic basis. In a later paper²⁷ they again demonstrated this phenomenon by studying the effect on the temperature of the skin and toes and the muscles of the calf of seven methods employed to alter the circulation in the lower extremities. In addition to the intravenous injection of typhoid vaccine, these methods consisted of (1) lumbar paravertebral injections of alcohol, (2) spinal anesthesia, (3) intravenous injections of a hyper-

26 Friedlander, M., Bierman, W., and Silbert, S. Temperature Changes in Skin and Muscle of Lower Extremities Following Intravenous Injections of Typhoid Vaccine, *Proc Soc Exper Biol & Med* **41** 221 (May) 1939.

27 Friedlander, M., Silbert, S., and Bierman, W. Regulation of Circulation in the Skin and Muscles of the Lower Extremities, *Am J M Sc* **199** 657 (May) 1940.

tonic solution of sodium chloride, (4) intravenous injections of physiologic solution of sodium chloride, (5) intravenous injection of epinephrine, and (6) immersion of the forearms in hot water. With one exception, all the methods employed produced increase in the temperature of the skin, with reverse or no changes in the muscles. Hypertonic solution of sodium chloride was unique in its ability to increase the circulation in both the skin and the muscles. Although the temperature of the muscles did increase, the amount was slight, being approximately 25 per cent of that in the skin. This should be considered a small rise when one considers the mild dilatation produced by hypertonic solution of sodium chloride alone. A similar rise in temperature of the muscles followed the administration of epinephrine, but the cutaneous temperature was lowered. Sympathetic paralysis failed to increase the circulation of the muscles, thus, little physiologic basis was furnished for ganglionectomy in the treatment of intermittent claudication. The same might be said for all the other methods, with the possible exception of injection of a hypertonic solution of sodium chloride and of epinephrine.

Haury²⁸ was able to demonstrate vasodilatation in the extremities of 7 patients following the intravenous administration of magnesium sulfate. A glass oncometer was used to determine the presence of vasodilatation. The usual dose was 20 cc of a 10 per cent solution, and dilatation persisted for ten to thirty minutes. In 1 case of Raynaud's disease the usual intravenous injection was supplemented by intramuscular injection of 2 cc of a 50 per cent solution of magnesium sulfate, and the patient reported relief of symptoms for twenty-four hours. As symptoms in Raynaud's disease occur in episodes, this result means little. It has been the experience of this author that this salt should be used with great caution, as serious consequences are not uncommon.

The action of nicotinic acid on the peripheral circulation was again studied by Popkin.²⁹ Fifteen adults were given 30 to 120 mg of nicotinic acid by mouth. As had previously been noted, the majority of patients had transitory flushing of the skin, tingling, itching and sensation of heat, regardless of the condition of the subject or the size of the dose. Changes in the surface temperature of the face, fingers and toes were variable and unpredictable. The amplitude of the oscillometric tracings was diminished, varying directly with the quantity administered. The authors agreed that the effects of nicotinic acid were similar to those produced by histamine and of little value in the therapy of peripheral vascular diseases.

28 Haury, V. G. The Effect of Intravenous Injections of Magnesium Sulfate on the Volume of the Extremities, *J Lab & Clin Med* **24**:951 (June) 1939.

29 Popkin, R. J. Nicotinic Acid. Its Action on the Peripheral Vascular System, *Am Heart J* **18** 697 (Dec) 1939.

Theis and Freeland³⁰ studied the effect of intravenous administration of sodium tetrathionate and sodium thiosulfate on normal persons and patients with peripheral vascular diseases, particularly those with thromboangitis obliterans. In many cases there was increase in peripheral temperature, decrease in pulse rate and reduction in blood pressure. Changes in oxygen capacity and oxygen saturation of the arterial and venous blood were noted. Changes in oxygen saturation, however, were not as marked in patients with thromboangitis obliterans as they were in the control group or in patients with other types of circulatory disease. The effects of these two drugs were noted to have an effect opposite that of tobacco. They were therefore concluded to be of value in treatment of thromboangitis obliterans, but no mention was made of the therapeutic results.

Cohen and Rosen³¹ demonstrated dilatation of the capillaries and arterioles of the web of the frog's foot after the application of various ointments containing acetylbetamethylcholine chloride. With ointments containing histamine hydrochloride dilatation was noted only in the capillaries, with general constriction of the arterioles. Clinically these ointments produced a satisfactory erythema in all patients to whom they were applied. They were found to be more effective when used in compound ointment of menthol base, and heat was found to enhance their action. Beneficial results were obtained in patients with arthritic pains presumably secondary to coexisting circulatory disturbances.

Reynolds and Foster³² observed the effect of estrogenic substance on the blood vessels of the rabbit's ear. Direct visualization and temperature studies were made. The authors concluded that this hormone caused dilatation of the minute vessels, not, however, of maximal degree. They noted that the rate of blood flow through the ear varied, not with the degree of vasodilatation brought about by the estrogen but with the requirements for heat loss which dilatation of the smaller vessels imposed in the regulation of normal body temperature under various experimental conditions.

A clinical study followed in which the authors³³ noted the effects of estrogen on the peripheral circulation by observing the changes in

30 Theis, F. V., and Freeland, M. R. Thromboangitis Obliterans. Treatment with Sodium Tetrathionate and Sodium Thiosulfate, *Arch Surg* **40** 190 (Feb) 1940.

31 Cohen, A., and Rosen, H. Mecholyl and Histamine Effects on Peripheral Circulation and Relief of Arthritic Pain, *Arch Phys Therapy* **21** 12 (Jan) 1940.

32 Reynolds, S. R. M., and Foster, F. I. Peripheral Vascular Action of Estrogen, Observed in the Ear of the Rabbit, *J Pharmacol & Exper Therap* **68** 173 (Jan) 1940.

33 Reynolds, S. R. M., and Foster, F. I. Peripheral Vascular Action of Estrogen in the Human Male, *J Clin Investigation* **18** 649 (Nov) 1939.

cutaneous temperature and finger volume following the injection of estrogen in 20 normal men. Observations on the effect of single injections of the estrogen were made on all subjects, with the exception of 3 who received two injections and 1 who received nine injections. Approximately two thirds of the patients showed an effect involving an increase in finger volume, which commenced a few minutes after the injection and continued from thirty to sixty minutes. The average increase in finger volume was 4.6 per cent. No change in cutaneous temperature was observed. Injection of an unknown substance, corn oil, as a vehicle had no such effect on finger volume in these subjects. The character of the response, with other established facts regarding the vascular effects of estrogen, indicated that it depended on dilatation of the small vessels in the skin beyond the arterioles. There was no measurable increase in the rate of blood flow in the skin. The failure of estrogen to bring about dilatation of the cutaneous vessels in some subjects was unexplained.

Thomas³⁴ repeated the existing experimental studies on the effect of theelin and testosterone propionate on the incidence of gangrene of the rat's tail induced by ergotamine tartrate. He found that neither substance affected or altered the gangrene of either male or female rats.

For determining the effect of massive doses of insulin on the peripheral circulation of 7 patients with schizophrenia, Abramson and his colleagues³⁵ used the plethysmographic method. They stated that a marked increase in blood flow was usually observed in the hand, forearm and leg at the height of the hypoglycemic response. When the hypoglycemia was terminated by the administration of carbohydrate, a rapid decrease in blood flow to below the control level usually occurred, especially in the hand. When dextrose was given without the previous injection of insulin, this effect on the blood flow was not apparent.

During the hypoglycemic state, when the blood flow to the arm was increased about two and three-tenths times, the blood from the forearm showed a significant decrease in arteriovenous differences for both oxygen and carbon dioxide. From chemical changes of the same magnitude in both blood from the brain and that from the arm, previous workers have concluded that there is no significant change in cerebral blood flow during the hypoglycemic state. From these studies, however, one notes the necessity for obtaining simultaneous changes in the blood flow and in the chemical constituents for proper evaluation of the data.

34 Thomas, R. M. Sex Hormone Therapy in Experimental Peripheral Gangrene, *Yale J Biol & Med* **12** 415 (March) 1940.

35 Abramson, D. I., Schkloven, N., Margolis, M. N., and Mirsky, I. A. Influence of Massive Doses of Insulin on Peripheral Blood Flow in Man, *Am J Physiol* **128** 124 (Dec) 1939.

DeBakey, Burch and Ochsner³⁶ studied the effect on the peripheral pulse volume of ligation of a vein and chemical irritation of a venous segment. This study was made on the hindfeet of 12 dogs, and the measurements were determined with the plethysmograph. After the ligation of the main veins of the hindleg the volume of pulsation diminished markedly (52.5 per cent). It was also observed that the venous pressure increased from a mean value of 7.7 cm. of water before ligation to one of 97.0 cm. after ligation. This effect was not influenced by the presence or the absence of the sympathetic ganglions and the intervening chain.

When a segment of the main vein was chemically irritated by injection either into the lumen or in the perivascular tissues, a marked diminution of the peripheral pulse volume (51.6 per cent) occurred. In these experiments the interruption of nerve pathways either by local infiltration of procaine hydrochloride at the site of the irritation or by resection of the lumbar sympathetic ganglions and chain abolished this effect. This suggested that the decrease in the volume of pulsations following chemical phlebitis or periphlebitis was due to vasoconstrictor impulses initiated locally by the chemical irritant and coursing through the sympathetic ganglions to reach the terminal arterial vessels of the extremity.

Fatherree, Adson and Allen,³⁷ in continuing their work on the effect of epinephrine on smooth muscle after sympathectomy, concluded that both preganglionic and postganglionic section for Raynaud's disease of the hands caused increased sensitivity of the arteries to epinephrine, but that the degree of increased sensitivity was the same in the two instances. This is contrary to previously reviewed articles, in which it was maintained that preganglionic section for Raynaud's disease produced better clinical results than ganglionectomy, because the former operation did not greatly increase sensitivity to epinephrine while the latter did. After sympathectomy for Raynaud's disease of the lower extremities the authors found little increase in sensitivity of the digital arterioles to epinephrine. Even though this was in keeping with clinical results, Fatherree and his colleagues were unable satisfactorily to explain the occasional unfavorable result in cases of Raynaud's disease of the hands on the basis of sensitivity of the arterioles to epinephrine.

36 DeBakey, M., Burch, G. E., and Ochsner, A. Effect of Chemical Irritation of a Venous Segment on Peripheral Pulse Volume, *Proc. Soc. Exper. Biol. & Med.* **41**: 585 (June) 1939.

37 Fatherree, T. J., Adson, A. W., and Allen, E. V. The Vasoconstrictor Action of Epinephrine on the Digital Arterioles of Man Before and After Sympathectomy, *Surgery* **7**: 75 (Jan.) 1940.

Steck and Gellhorn³⁸ studied the effect of the inhalation of oxygen-deficient gas mixtures and of carbon dioxide in air on the peripheral blood flow in the hand of sympathectomized patients. Previously reviewed articles have shown that carbon dioxide regularly reduces the blood flow in normal persons. This reaction did not occur after sympathectomy. The flow remained essentially unchanged with low concentrations of carbon dioxide, but with higher concentrations the flow was increased. It was the opinion expressed by the authors that this increased flow was due to the increased blood pressure and dilating action of carbon dioxide on the peripheral blood vessels, which is unopposed by the normally present and increased sympathetic impulses originating in the vasomotor center. They were unable to determine the presence or absence of sympathetic impulses by this method.

Zothe³⁹ suggested the therapeutic use of strophanthin in cases of peripheral vascular disturbances. When this drug was given intravenously in therapeutic doses improvement of the depressed muscular contraction occurred. This beneficial effect was attributed to better utilization of oxygen by the tissue rather than to increased blood flow.

Effect of Tobacco—Abramson, Zazeela and Oppenheimer⁴⁰ continued their plethysmographic studies of blood flow in the hand, forearm and foot. These investigations showed that smoking caused a decrease in peripheral blood flow, which took place, however, only in the blood vessels of the skin, and not in those of voluntary muscle. This constrictor response observed in the cutaneous vessels of the hand cannot therefore be considered as typical of reactions of blood vessels elsewhere in the body. These findings again emphasize the independent action of the arteries of the skin and of the muscles.

The relationship between tobacco and peripheral vasospasm was again studied by Moyer and Maddock⁴¹. Twenty subjects were observed during smoking. In all cases a progressive decrease in cutaneous temperature was noted. The period of recovery following cessation of smoking was variable, in no case was it less than five or more than seventy minutes. It was found that the temperature of the fingers

38 Steck, I. E., and Gellhorn, E. The Effect of Carbon Dioxide Inhalation on the Peripheral Blood Flow in the Normal and in the Sympathectomized Patient, *Am Heart J* **18** 206 (Aug.) 1939.

39 Zothe, H. Untersuchungen über die Wirkung des Strophanthins bei peripheren Durchblutungsstörungen, *Ztschr f Kreislaufforsch* **30** 889 (Dec.) 1938.

40 Abramson, D. I., Zazeela, H., and Oppenheimer, B. S. Plethysmographic Studies of Peripheral Blood Flow in Man. III. Effect of Smoking upon the Vascular Beds in the Hand, Forearm and Foot, *Am Heart J* **18** 290 (Sept.) 1939.

41 Moyer, C. A., and Maddock, W. G. Peripheral Vasospasm from Tobacco, *Arch Surg* **40** 277 (Feb.) 1940.

returned to normal more rapidly than did that of the toes, the difference in the time being as much as three minutes in some cases. After a second cigaret the changes described again occurred.

The possibility that the alteration in rate, rhythm and depth of breathing incident to smoking might have produced these changes was discarded, as no changes occurred when the subjects were asked to simulate smoking by puffing on a small paper tube or an empty pipe. The possibility that they were due to carbon monoxide was found not to hold when no vascular response could be elicited with cubeb cigaets. Cardiovascular changes occurred to a lesser degree when the smoke was filtered through two bottles or through a layer of cotton impregnated with ferric chloride. Some of the subjects studied had far advanced occlusive vascular disease, but vasoconstriction could still be demonstrated after smoking.

As a direct proof that nicotine was the principal activator of this vasomotor response, 0.1 mg. of the drug injected intravenously produced marked peripheral vasoconstriction. No response was obtained when nicotine was given by mouth, even though 1 mg. was given every ten minutes for six doses. Apparently an insufficient quantity was absorbed into the blood stream to produce cardiovascular response.

In spite of this evidence, Mulinos and Shulman⁴² asserted that the deep breathing usually associated with smoking is a factor in vasoconstriction. They used five methods to analyze the response of blood vessels to smoking and deep breathing. The rate of blood flow was studied with the pressure plethysmograph of Hewlett and Van Zwaluwenburg. Changes in volume were measured with a single plethysmograph, and a skin calorimeter was used as an indicator of the available heat in the skin. The remaining two methods consisted of thermopile studies of cutaneous temperature and capillary microscopy. Deep breathing alone could account for the decreased rate of blood flow, loss of hand volume and visible capillary changes equally as well as could smoking. In studies of cutaneous temperature both deep breathing alone and smoking decreased the temperature, but in the majority of cases a greater fall occurred after smoking. The subjects who did not inhale cigaret smoke showed a greater vascular response of the hand from ten deep breaths than from the puffing and a lesser response than did those who inhaled the cigaret smoke. Inhaling the smoke from denicotinized cigaets resulted in as great vasoconstriction as inhaling the smoke from a standard brand cigaret, and occasionally the response was greater. Although these findings of Mulinos and Shulman are not compatible with those reported in the majority of articles, it is interesting

42 Mulinos, M. G., and Shulman, I. The Effects of Cigarette Smoking and Deep Breathing on the Peripheral Vascular System, *Am J M Sc* **199** 708 (May) 1940.

to note the response of deep breathing alone on the peripheral vascular system. One wonders if these authors request their patients to refrain from deep breathing because of its vasoconstricting effect.

Harkavy⁴³ summarized all of his work on cutaneous reactions to tobacco and answered the many criticisms. The incidence of cutaneous reactions to tobacco was studied in (1) 400 normal smokers, both male and female, (2) 126 women nonsmokers, (3) 319 control smokers, consisting of 47 normal persons and 292 adult patients suffering from various ailments, (4) 140 patients with thromboangitis obliterans, (5) 31 patients with peripheral vascular disease associated with arteriosclerosis, and (6) 100 patients with coronary disease and angina pectoris. These studies indicated that positive cutaneous reactions to tobacco (prepared according to a method that the author described) represent a true immunologic response. This was demonstrated by (1) the presence of tobacco reagins in patients reacting positively, (2) the specific absorption of these reagins by corresponding tobacco allergens in patients with multiple sensitization and (3) the induction of a characteristic local eosinophilic reaction in the immediate cutaneous response of patients with thromboangitis obliterans, disease of the coronary arteries and migrating phlebitis tested intradermally with tobacco. This was further attested experimentally, in that 33 per cent of male rats given daily intraperitoneal injections of the same tobaccos employed in testing the patients had gangrene of the toes. These animals were shown to be sensitized to tobacco by the Schultz-Dale technique. Of the 140 patients with thromboangitis obliterans tested with ragweed and timothy pollen, horse dander and tobacco, 68 per cent gave positive reactions of 1 plus and over to tobacco alone, and 44 per cent of these had reagins for tobacco. An additional 10 per cent gave plus-minus reactions, making a total of 78 per cent, the patients with thromboangitis obliterans reacting to tobacco only. This is in contrast to the 9 per cent of 400 normal control smokers who gave reactions to tobacco only. Twelve patients with thromboangitis obliterans tested with nicotine tartrate in 1:10,000 and 1:5,000 concentrations gave completely negative reactions. Of the 100 patients with disease of the coronary arteries and angina pectoris, 44 per cent reacted to tobacco and 10 of 14 had reagins to tobacco. Harkavy inferred from these observations that tobacco allergy plays an important part in certain forms of vascular disease as well as in symptoms referable to other systems, such as the respiratory, the gastrointestinal and the cutaneous. The positive reactions assume etiologic significance, since they can be correlated with the fact that in the patients studied, particularly those with thromboangitis obliterans or angina pectoris, with or without disease of the coronary

43 Harkavy, J. Tobacco Skin Reactions and Their Clinical Significance, *J Invest Dermat* 2:257 (Oct) 1939.

arteries, resumption of smoking called forth an exacerbation of all symptoms. Although it has been impossible to adduce any demonstrable proof of sensitization to nicotine as such, the question of hypersensitiveness to its alkaloid on theoretic grounds cannot be dismissed completely. Sensitiveness to drugs and chemicals may exist irrespective of cutaneous reactions. Aside from the possible sensitizing effect of nicotine, the pharmacologic action of the drug in all probability plays an accessory part through its constrictive influence on blood vessels, with consequent diminution in blood flow in the tissues involved. Such a result, common in all smokers, is, however, transitory in normal persons. In itself the drug evokes no notable symptoms, but it may become of utmost importance in the evolution of pathologic tissue changes in persons allergic to tobacco. In the latter, hypersensitiveness to tobacco may possibly intensify the pharmacologic action of nicotine. The immunologic and clinical evidence presented suggests that tobacco has an inciting role in thromboangitis obliterans and in certain types of involvement of the coronary arteries.

Silbert⁴⁴ reported a case of angioneurotic edema in a 44 year old man who had thromboangitis obliterans. He was a heavy smoker, and cutaneous tests revealed him to be markedly sensitive to tobacco. With cessation of the use of tobacco he had no attacks of angioneurotic edema and the peripheral symptoms disappeared. This case is of interest because it lends support to Haikavsky's work.

Cases of acute and chronic nicotine poisoning in 24 men between the ages of 17 and 53 were reported by Weicker.⁴⁵ These men smoked between fifteen and fifty cigarettes daily. Most of the patients had disease of the coronary arteries in the form of angina pectoris or cardiac infarcts. Thromboangitis was observed in 4 men. In 2 of these, nicotine was the only demonstrable external factor capable of impairing the peripheral circulation, and in the other 2 exposure to cold and dampness may have played a part.

ARTERIOSCLEROSIS

Wilder⁴⁶ compared his views on the relation of diabetes to arteriosclerosis with those of other authors. From a study of necropsy material he concluded that sclerotic lesions of the arterioles and finer arteries do not occur with greater frequency or greater intensity in cases of diabetes than in those of other diseases, that the frequency of sclerosis of the longer arteries also was not unusual in cases of diabetes, but that the intensity of the process and the incidence of severe grades

44 Silbert, S. Angioneurotic Edema Due to Tobacco Sensitivity and Thrombo-Angitis Obliterans in the Same Patient, *J. A. M. A.* **114** 1442 (April 13) 1940.

45 Weicker, B. Kreislaufschaden und Nicotin, *Deutsches Arch. f. klin. Med.* **185** 393, 1940.

46 Wilder, R. M. Diabetic Arteriosclerosis, *Internat. Clin.* **2** 13 (June) 1939.

of atheromatosis and of occlusion of the lumen of the arteries of the heart and legs were significantly greater in persons with diabetes than they were in persons who were not diabetic. Women with diabetes seemed to be much more susceptible to severe grades of occlusive lesions than other women, an observation for which no explanation was apparent. Although other authors have shown that the long duration of diabetes is attended with more progression of atherosclerosis in the heart and legs than can be attributed simply to aging, Wilder expressed the belief that there is no correlation between the severity of the diabetes and that of the atherosclerosis. The contrary was also shown to be true, as many patients with diabetes of long duration remain free from clinically detectable evidence of atherosclerosis and at necropsy present no greater degree of atheroma or other disease of the arteries than is commensurate with the degree of physiologic senile arteriosclerosis to be expected in persons of their age.

The observations of Wilder are not entirely in keeping with those of Bowen, Regan and Koenig⁴⁷. They studied the vascular status of 52 diabetic patients who had been under observation for a period of ten to thirteen years. The patients were divided into three groups: group 1, those who had excellent or good care throughout most of their diabetic life; group 2, those who were regarded as uncooperative; and group 3, those whose diabetes had not been controlled during the period before insulin treatment, with resulting undernourishment from a low caloric diet or very severe diabetes, but whose disease had been well controlled since insulin treatment was begun. Blood pressure studies revealed that there was no correlation between the height of the blood pressure and the impairment of the circulation of the lower extremities.

The authors concluded from their observations that atherosclerosis of the lower extremities could be prevented or delayed by controlling the diabetes continuously, provided the control was started early enough after the inception of the disease. Atherosclerosis of the lower extremities did not develop in persons whose diabetes was controlled, even though the diet was moderately high in fat. An increase in body weight appeared to favor atherosclerosis of the lower extremities, but since in most instances this was associated with poor control of the diabetes it was impossible to appraise the effect of stoutness. In a small series of patients no relationship existed between the degree of atherosclerosis of the lower extremities and the complicating coronary occlusion. Coronary occlusion seemed to be favored by stoutness. Eleven of the patients showed lack of parallelism between calcification of the arteries of the lower extremities and the state of the circulation. The authors

47 Bowen, B. D., Regan, J. S., and Koenig, E. C. The Development of Arteriosclerosis in the Diabetic, Based on the Study of a Group of Patients During Ten to Thirteen Years, *Ann Int Med* **12** 1996 (June) 1939

expressed the belief, however, that the demonstration of calcification of the arteries must be regarded as accessory evidence of atherosclerosis, which may be assumed if a patient has had uncontrolled diabetes for some time. Five of the patients had had calcification of the arteries of the lower extremities for thirteen years.

Barker⁴⁸ studied the plasma lipoids in a series of 73 patients with arteriosclerosis obliterans without diabetes mellitus and compared them with a control series of 200 subjects of various ages who were considered normal. The ranges for the total lipoids and the various lipid fractions were essentially the same in the two groups. These lipid fractions consisted of cholesterol, cholesterol esters, phospholipids and fatty acids. The mean values for all the fractions and for the total lipoids were, on the other hand, definitely and significantly higher in patients with arteriosclerosis than in the control group. Barker expressed the opinion that since the plasma lipoids have been shown to be essentially normal in cases of thromboangitis obliterans, these high values for plasma cholesterol and total lipoids might be of a diagnostic aid in cases in which differentiation between the two entities is difficult. Diets low in animal fats were given 8 patients with arteriosclerosis obliterans having comparatively high lipid levels, with consequent lowering of the level in 4 of them. Barker has now observed 3 cases in which arteriosclerosis obliterans, xanthoma tuberosum and marked lipema occurred together. A detailed description of 2 of these cases was reported previously by the same author.⁴⁹

The functional state of a vessel wall was found to influence the incidence and severity of experimental arteriosclerosis. Harrison⁵⁰ performed unilateral lumbar sympathectomy on a series of rabbits, which were subsequently fed large doses of cholesterol in oil. A control group received the same diet, but no operative intervention. Studies of the cutaneous temperatures were constantly employed during the experiment to make sure of the presence of dilatation in the sympathectomized extremity. At the completion of the experiments, Harrison found the vascular lesions in the extremity on the side of operation to be more severe than those of the opposite extremity. In the control animals there was no significant difference between the two extremities. Chemical estimations of the amount of cholesterol deposited in the vessels

48 Barker, N. W. The Plasma Lipoids in Arteriosclerosis Obliterans, *Ann Int Med* **13** 685 (Oct) 1939.

49 Barker, N. W. Occlusive Arterial Disease of the Lower Extremities Associated with Lipemia and Xanthoma Tuberosum, *Ann Int Med* **12** 1891 (May) 1939.

50 Harrison, C. V. Effect of Sympathectomy on Development of Experimental Arterial Disease, *J Path & Bact* **48** 353 (March) 1939.

confirmed his observations. Harrison thus concluded that sympathetic paralysis enhances the effect of cholesterol in producing experimental arteriosclerosis.

Temporal Arteritis—Two cases of temporal arteritis were reported by Dick and Freeman,⁵¹ making a total of 13 such cases now recorded in the literature. In all of these cases the authors have described a similar syndrome. The disease occurs chiefly in old people, the average age being 67. Weakness and general malaise prior to and during the local involvement of the arteries about the head were noted. The period of prodromal symptoms varied from two weeks to eight months, although it was not always clear whether the contiguous signs and symptoms were related to this disease. All of the patients had headaches, which were often throbbing and associated with tenderness of the scalp and painful mastication. The swelling and redness of the periarterial tissues usually followed the onset of the headache. Fever was invariably present. The disease usually ran a self-limiting course, lasting several months. Although temporal arteritis has some similarity to periarteritis nodosa, thromboangiitis obliterans and rheumatic arteries, its cause remains obscure. The pathologic picture is that of simple arteritis, however, Dick and Freeman noted giant cells in the inflammatory process. Because of the age incidence, the syndrome is probably related to degenerative vascular changes with a superimposed infection.

ANEURYSM

The absence of pulsations in the radial and carotid arteries was noted by Maurer⁵² in 2 cases of aneurysm of the aortic arch.

Yater⁵³ reported 4 cases of ruptured popliteal aneurysms following trivial or unnoticed trauma. It was interesting to note that the pathologic study in all these cases revealed severe degenerative changes of a nonspecific nature, whereas all the patients had syphilis.

THROMBOANGIITIS OBLITERANS

An excellent article on the diagnosis and management of chronic obliterative vascular disease was submitted by McKittrick⁵⁴. Although most of the material in his article has been mentioned in former reviews,

51 Dick, G. F., and Freeman, G. Temporal Arteritis, *J. A. M. A.* **114** 645 (Feb. 24) 1940.

52 Maurer, E. Absence of Pulse in the Vessels of the Upper Extremities and Neck in Aneurysm of the Aortic Arch, *Am. Heart J.* **17** 716 (June) 1939.

53 Yater, W. M. Ruptured Popliteal Aneurysm. Report of Four Cases, *Am. Heart J.* **18** 471 (Oct.) 1939.

54 McKittrick, L. S. The Diagnosis and Management of Chronic Obliterative Vascular Disease, *J. A. M. A.* **113** 1223 (Sept. 23) 1939.

one observation is worthy of note. In the differential diagnosis of thromboangitis obliterans and arteriosclerosis the age of the patient and the roentgenographic evidence of calcification in the vessels play a major role in diagnosis. A definite diagnosis of thromboangitis obliterans can usually be made in a man 40 years of age or younger, with symptoms of years' rather than of months' duration, without the roentgenographic evidence of calcification and with a normal sugar content of the blood. A probable diagnosis can be made in a man between the ages of 40 and 55 with symptoms of more than one year's duration and with slight or no evidence of calcification, particularly if there is evidence of involvement of an upper extremity. A diagnosis of this disease is rarely made in a patient over 55 years of age, with or without roentgen evidence of calcification and with a history of less than one year's duration. McKitttrick stated that he would be unwilling to make a diagnosis of thromboangitis obliterans in a woman over 40. The diagnosis of arteriosclerosis was usually made in the older age groups. In 30 per cent of 66 proved cases roentgenographic evidence of calcification was lacking. A diagnosis of arteriosclerotic obliterative disease may be made with reasonable certainty in a patient 55 years of age or over with symptoms of less than one year's duration and with roentgenographic evidence of calcification. The author expressed the belief that it is impossible to make a positive diagnosis in a man between the ages of 40 and 55 with symptoms of approximately a year's duration and with little or no evidence of calcification on roentgen examination. As the combination of diabetes and thromboangitis obliterans is rare, McKitttrick stated that he feels justified in making a diagnosis of so-called diabetic gangrene in the case of any patient, male or female, with definite evidence of obliterative arterial disease associated with diabetes.

Hausner and Allen⁵⁵ commented on the generalized arterial involvement in thromboangitis obliterans. In 57 per cent of a group of 500 patients who had this disease, the coronary arteries were diseased. Two per cent had clinical evidence of cerebrovascular involvement, and 3 cases had abdominal involvement. All these cases have been previously reported and included in former reviews. In 1 case the pulmonary artery and the peripheral arteries were affected. Hausner and Allen reviewed the literature and found reports of involvement of the renal, splenic, spermatic, carotid, retinal, adrenal, pancreatic, duodenal, hepatic and prostatic arteries, as well as of the aorta. They concluded that thromboangitis may be a widespread disease, but that when the arterial lesions

55 Hausner, E., and Allen, E. V. Generalized Arterial Involvement in Thrombo-Angitis Obliterans Including Report of a Case of Thrombo-Angitis Obliterans of a Pulmonary Artery, *Proc Staff Meet*, Mayo Clin **15** 7 (Jan 3) 1940.

are outside the extremities they are almost always degenerative, in contrast to the inflammatory nature of the vascular lesions in the extremities

Wagener⁵⁶ presented an interesting review of disease in the walls of the retinal vessels, associated with recurrent hemorrhagic extravasations into the vitreous. He stated the opinion that in a certain number of cases of this condition, particularly of the perivenous type, the disease may be due to tuberculosis, however, in a larger number in which tuberculosis cannot be demonstrated elsewhere in the body, a primary nonspecific inflammatory or degenerative lesion of the vessel wall should be suspected. This lesion, he asserted, may well be the retinal counterpart of thromboangitis obliterans and may be confined to the retinal vessels, or at times be associated with similar lesions in other parts of the body.

RAYNAUD'S DISEASE

Leys⁵⁷ described a case of diffuse scleroderma and Raynaud's syndrome resulting from the use of the pneumatic hammer. The description of the case was too brief for confirmation, but the author expressed the opinion that injury from the pneumatic hammer was purely incidental to the other two conditions, although it might have aggravated existing conditions.

A condition resembling Raynaud's disease was described by Oberdorffer⁵⁸ in a 30 year old woman suffering from leprosy. The patient had attacks of blackness of the tips of the fingers with coldness which subsided in two weeks, leaving acroteric areas. Although few data were given to establish the diagnosis, the case is reported as one of pseudo Raynaud's disease.

PERIARTERITIS NODOSA

The majority of articles concerned with periarteritis nodosa still consist of case reports, each usually supporting one of the many etiologic theories.

Harris, Lynch and O'Hare⁵⁹ reported 6 additional cases of proved periarteritis nodosa. They noted that prior to June 1, 1938, only 101 cases had been reported in the English literature. These cases were

56 Wagener, H. P. Thrombo-Angitis of the Retinal Vessels, *Am J M Sc* **199** 296 (Feb) 1940.

57 Leys, D. Diffuse Scleroderma and Raynaud's Phenomenon from Use of Pneumatic Hammer, *Lancet* **2** 692 (Sept 23) 1939.

58 Oberdorffer, M. J. Pseudo-Raynaud's Disease in Leprosy, *Internat J Leprosy* **7** 395 (July-Sept) 1939.

59 Harris, A. W., Lynch, G. W., and O'Hare, J. P. Periarteritis Nodosa, *Arch Int Med* **63** 1163 (June) 1939.

studied, and the frequencies of symptoms, signs and abnormal laboratory findings were tabulated. They were unable to answer the question of causation. A history of allergy was obtained in only 15 per cent of the cases, which is not sufficient to substantiate the proposed theory of an allergic origin. The infrequency of pains in the joints and other arthritic manifestations is worthy of mention. Nothing could be added to the pathologic picture, as it appears to be well established. Although there were 26 antemortem diagnoses in the 101 cases, an analysis of the clinical symptoms and signs did not reveal a characteristic clinical pattern. The order of frequency of the more significant symptoms and signs were as follows: fever, leukocytosis, albuminuria, rapid onset, abdominal pain, edema, loss of weight, hematuria and neuritis. Of the 101 patients, 10 were reported as "recovered," indicating that the disease is not "100 per cent fatal."

Additional cases were reported by Fitz, Parks and Branch,⁶⁰ Sawyer,⁶¹ Emerson, Schroeder and Maynard,⁶² Cleland,⁶³ Allen,⁶⁴ Trasoff and Scarf,⁶⁵ Weir,⁶⁶ and Matras.⁶⁷ The report by the last-mentioned author is of interest in that the pathologic changes were confined to the skin.

THROMBOSIS AND EMBOLISM

Lueth⁶⁸ reported 4 cases of thrombosis of the abdominal aorta. Although this disorder is relatively infrequent, it is by no means a rare clinical entity. Diagnosis was difficult because of the variability of symptoms. Lueth stated that its recognition was dependent on the rapidity and extent of arterial closure of the aorta. The slower the

60 Fitz, R., Parks, H., and Branch, C. F. *Periarteritis Nodosa*, *Arch Int Med* **64** 1138 (Dec.) 1939.

61 Sawyer, C. F. *Necrotizing Arteritis (Periarteritis Nodosa)*, *Surgery* **6** 717 (Nov.) 1939.

62 Emerson, R. S., Schroeder, H. A., and Maynard, E. P., Jr. *Periarteritis Nodosa. Its Clinical Recognition with Report of Illustrative Case*, *Brooklyn Hosp J* **1** 107 (April) 1939.

63 Cleland, J. B. *Periarteritis Nodosa, with Report of Two New Cases*, *M. J. Australia* **1** 846 (May 14) 1938.

64 Allen, P. D. *Periarteritis Nodosa Simulating an Acute Abdominal Condition Requiring Operation*, *Arch Surg* **40** 271 (Feb.) 1940.

65 Trasoff, A., and Scarf, M. *Periarteritis Nodosa and Asthma*, *J Allergy* **11** 277 (March) 1940.

66 Weir, D. R. *Polyarteritis Nodosa. Report of Case*, *Am J Path* **15** 79 (Jan.) 1939.

67 Matras, A. *Zur kutanen Form der Periarteritis Nodosa*, *Wien klin Wchnschr* **51** 991 (Sept 16) 1938.

68 Lueth, H. C. *Thrombosis of the Abdominal Aorta. A Report of Four Cases Showing the Variability of Symptoms*, *Ann Int Med* **13** 1167 (Jan.) 1940.

formation of obstruction, the more delayed the onset of symptoms. Absence of peripheral pulsation was not necessarily diagnostic. Sharp shooting pains in the legs, abolition of femoral, popliteal or posterior tibial pulsations, and ascending gangrene of the legs were cited as supportive evidence. Coincident with the arrest of flow to the legs there were frequently symptoms resulting from ischemia of the spinal cord.

Lueth stated the opinion that the symptoms last mentioned had not received sufficient attention. The coincidence has been demonstrated repeatedly in many laboratories in a variety of animals. Anatomically it is logical, as many of the branches of the lower abdominal aorta go to the spinal cord.

Fry⁶⁹ also reported 3 cases of embolism and thrombosis of the abdominal aorta. His patients survived from one to five years after the onset of occlusive symptoms. In only 1 of the patients did gangrene develop, in spite of the high level of occlusion. Because of the slow onset the symptoms were minor, consisting of pain and, as Lueth stressed, symptoms of involvement of the cord, namely, disturbances in sensation and muscle power in the lower extremities.

Fetterman and Spitler⁷⁰ cited clinical examples of neuropathy due to defective blood supply to nerves. They expressed the opinion that involvement of the main arterial trunk to a nerve or simultaneous lesions in smaller branches (*vasa nervorum*) were responsible for such ischemic changes in the nerve. The literature on this subject was adequately reviewed, and cases of other authors, usually verified by pathologic studies, were discussed. Such lesions had been reported in cases of thromboangitis obliterans, arteriosclerosis, embolism, thrombosis, syphilis and periarteritis nodosa. In the cases described by Fetterman and Spitler, the neuropathy was thought to be due to vascular complications in the *vasa nervorum*. As the etiologic factor was obscure and pathologic studies were not obtainable, the final solution remained a matter of individual opinion.

Wolf and Levinsohn⁷¹ reported on an unusual arterial complication in an infant with mongolism and congenital heart disease (tetralogy of Fallot). Thrombosis involved the patent ductus arteriosus, the ascending aorta, the left common carotid artery and the left subclavian, axillary and brachial arteries.

69 Fry, F. W. Embolism and Thrombosis of the Abdominal Aorta, *Am Heart J* **18** 57 (July) 1939.

70 Fetterman, J. L., and Spitler, D. K. Vascular Disorders of Peripheral Nerves, *J. A. M. A.* **114** 2275 (June 8) 1940.

71 Wolf, I. J., and Levinsohn, S. A. Arterial Occlusion in the Left Upper Extremity on a Mongoloid Idiot with Congenital Heart Disease (Tetralogy of Fallot), *Am Heart J* **18** 241 (Aug.) 1939.

Gitlow and Goldmark⁷² described 2 cases in which the pathologic process was characterized by generalized capillary and arteriolar thrombosis. Clinically the 2 cases varied, in the first case there was purpura with capillary thrombi, and in the second, atypical verrucous endocarditis with lupus erythematosus.

Dunphy and Whitfield⁷³ discussed mesenteric vascular disease on the basis of a study of 30 cases. The etiologic factors were not sufficiently obvious clinically to be considered essential in the diagnosis of this condition. In many cases pathologic changes elsewhere had rendered the patients moribund before the abdominal vascular accident occurred. The authors divided the clinical manifestations into three groups: those which result from spasm or small, nonfatal occlusions of the mesenteric arteries, so-called abdominal angina or abdominal intermittent claudication, those which follow extensive occlusion of a mesenteric artery or vein, "mesenteric vascular occlusion," and those which are a consequence of the rupture of a sclerotic artery with peritoneal hemorrhage, "intra-abdominal apoplexy." In the cases of "abdominal angina" they noted a severe, deep-seated pain in the upper part of the abdomen, usually following meals. They expressed the belief that in the absence of abnormal roentgen findings one is justified in diagnosing this pain as of vascular origin. The most significant diagnostic feature of the second type is the marked contrast between the severity of the pain and the paucity of the physical findings. The pain is severe and persists after ordinary measures have been instituted for its relief. Frequently deep abdominal tenderness, more or less generalized, with rebound tenderness, can be elicited. In later stages peritonitis may develop. The leukocyte count and pulse rate were almost invariably elevated disproportionately to the temperature. Lastly, constipation, diarrhea and a variable amount of vomiting may develop.

Crile and Newell⁷⁴ reported a case of abdominal apoplexy in which the patient, who was known to be hypertensive, had spontaneous rupture of a sclerotic visceral vessel. The hemorrhage was controlled surgically. The authors wondered why this does not occur more frequently.

Three cases of dilatation and thrombosis of the subclavian artery resulting from abnormalities of the cervical and first thoracic ribs were reported by Eden⁷⁵. Evidence was brought forward to support the

72 Gitlow, S, and Goldmark, C. Generalized Capillary and Arteriolar Thrombosis, *Ann Int Med* **13** 1046 (Dec) 1939.

73 Dunphy, J. E., and Whitfield, R. D. Mesenteric Vascular Disease, *Am J Surg* **57** 632 (March) 1940.

74 Crile, G., Jr., and Newell, E. T., Jr. Abdominal Apoplexy. Spontaneous Rupture of a Visceral Vessel, *J A M A* **114** 1155 (March 30) 1940.

75 Eden, K. C. The Vascular Complications of Cervical Ribs and First Thoracic Rib Abnormalities, *Brit J Surg* **27** 111 (July) 1939.

76 Footnote omitted.

hypothesis that the vascular disease of the arm in these cases is due to damage to the wall of the subclavian artery by intermittent compression between the clavicle and the cervical or first thoracic rib. As a result, dilatation of the artery commonly occurs, with dense fibrosis around it and thrombosis. With continued trauma, a blood clot is thrown off in the form of emboli, which lodge in the vessels of the hand and arm, giving rise to progressive thrombosis and symptoms of vascular disease.

The author reviewed the literature on the vascular complications of cervical rib. There were fewer instances of vascular than of nervous complications. In the case of a vascular complication the simplest procedure is removal of the cervical rib. Division of the scalenus anterior muscle alone is insufficient to prevent further trauma. Enough of the abnormal rib is removed to allow the subclavian artery to pass freely beneath the clavicle without compression.

VEINS

Sampson, Saunders and Capp⁷⁷ studied the venous pattern of the anterior thoracic wall. The normal venous pattern was described. Prominent veins on the anterior wall of the chest were noted at all ages and were found to be extremely common after the age of 50 years. The authors expressed the opinion that most of these were produced by compression and partial obstruction of the subclavian vein between the clavicle and the first rib anterior to the scalene tubercle. Compression of the vein by tension on the clavipectoral fascia was given as an alternate explanation of the obstruction in this area. The prominent veins were thus considered to be collateral vessels, and in 1 case this was substantiated by visualization with diodrast.

In general, the authors were able, by a study of the venous pattern and the direction of blood flow, to differentiate this partial obstruction of the subclavian vein from obstruction of the innominate vein or the superior vena cava, and likewise from the distention of the veins of the chest which sometimes occurs during and after lactation.

The mechanism producing compression of the subclavian vein consisted of a projection of the first rib laterally and anteriorly against the backward and upward thrust of the clavicles. The type of person with prominent veins is, therefore, one with broad shoulders, and often a deep chest and erect posture, with shoulders held back. A high thoracic kyphosis or a slouched posture generally lowers the clavicles and moves them anteriorly, away from the ribs, preventing encroachment on the

⁷⁷ Sampson, J. J., Saunders, J. B. de C. M., and Capp, C. S. Compression of the Subclavian Vein by the First Rib and Clavicle, with Special Reference to the Prominence of Chest Veins as a Sign of Collateral Circulation, *Am Heart J* 19: 292 (March) 1940.

subclavicular space Thoracic scoliosis is often accompanied by asymmetric prominent veins, usually on the same side as the convexity of the spine

Partial obstruction of the subclavian arteries produces a thrill and murmur over the arteries, and occasionally lowering of the brachial blood pressure on that side Numbness of the arms occurred in 2 cases, and slight edema was present in 1 case

McLaughlin and Popma⁷⁸ reported a case of intermittent obstruction of the subclavian vein appearing with exercise During obstruction the entire extremity became swollen, blue and colder, and these changes were associated with a severe aching pain After rest the arm returned to normal Obstruction was demonstrated with thorium dioxide Mechanical pressure of the first rib on the vein during activity was believed to be responsible for this syndrome, as prompt and permanent cure followed section of the scalenus anterior muscle

Veal⁷⁹ studied the physiologic changes in an extremity produced by venous obstruction, the manner in which collateral vessels developed and the end results of such obstruction He noted that after obstruction of the large venous trunks there was a concomitant rise in the local venous pressure with retardation of the venous flow An associated arterial spasm was frequently noted, sufficient to produce severe pain and other signs of impaired arterial circulation As the changes in the lymphatic and tissue fluid circulation were secondary to the increased venous pressure, the amount of edema depended on the degree of elevation of this pressure Studies were made with venograms Veal concluded that collateral veins developed from preexisting veins and venules The newly developed collateral circulation was frequently found to fail because of its structural deficiencies, its superficial position and the long and devious course it often pursued The collateral veins were in many instances inadequate because they lacked valves If these veins were deep the squeezing effect of muscular action afforded compensation, but this could not take place if they were superficial To promote formation of deep collateral vessels, Unna boots (occlusive dressings of zinc oxide ointment) were suggested

Veal found that venographic studies and measurements of venous pressure were of considerable value in ascertaining the degree and extent of the venous obstruction Repeated studies of venous pressure, made at rest and during active exercise, provided the most accurate criterion of the progress of the formation of collateral venous circulation in the extremity

78 McLaughlin, C W, Jr, and Popma, A M Intermittent Obstruction of the Subclavian Vein, *J A M A* **113** 1960 (Nov 25) 1939

79 Veal, J R The Mode of Development of Collateral Venous Circulation in the Extremities, *Am Heart J* **19** 275 (March) 1940

Edwards and Edwards⁸⁰ studied histologically the valves in the upper ends of varicose saphenous veins and compared them with the valves of normal veins. Most of the varices were found either to be spontaneous in origin or to follow phlebitis of the deep veins, producing a variety of pathologic changes. In the two groups the valve cusps did not show profound intrinsic lesions. The fundamental lesion was found to be a dilatation of the commissural region, that is, the portion of the wall between the attachment of the valve cusps. This was shown to give rise to evagination of the wall and separation of the cusps, producing regurgitation of blood. A growth of fibromuscular tissue on the luminal surface of the dilated commissure was noted. The cusp itself showed extrinsic changes consisting of (1) relaxation with redundancy and kinking, (2) occasionally, rolling of the free margin of the cusp, and (3) in a few cases of severe involvement, distal eversion of the cusp.

In some of the normal veins early changes similar to those present in varicose veins were seen.

The authors concluded that the regurgitation of blood in the upper saphenous vein in the usual type of varicosity was secondary to relative insufficiency of the valves, dependent on the dilatation of the venous wall. In addition, they expressed the belief that the cause of varicose veins is to be sought in the disproportion between the venous pressure and the resistance of the wall of the vein. The usual type of varicosity was therefore not caused by local infection or inflammation, thrombophlebitis or spontaneous degeneration of valves.

Biegeleisen,⁸¹ in a study of 12 cases of so-called deep venous thrombosis with an radiopaque solution, observed no evidence of complete and lasting blockage. There was found in each case an adequate deep circulation, both from the clinical and from the roentgenographic point of view. He was unable to account for the increase in size of the involved extremity other than that due to the increase in area of the venous bed which consisted mainly of extensive collateral vascularization. As in many of these cases the condition had previously been considered "deep venous block," the injection of any of the superficial varicosities was contraindicated. Injection of these veins was in many cases found to be beneficial, and rightly so, as the studies in this series of cases clearly demonstrated patency of the deep veins. Luke⁸² came to similar conclusions. He questioned the existing axiom that

80 Edwards, J. E., and Edwards, E. A. The Saphenous Valves in Varicose Veins, *Am Heart J* **19** 338 (March) 1940.

81 Biegeleisen, H. I. Unilateral Enlargement of Lower Extremity Accompanying Varicose Veins, with Roentgen Studies of "Deep Venous Block," *Am J Roentgenol* **42** 683 (Nov) 1939.

82 Luke, J. C. The Venous Circulation in the Varicose Extremity and Its Practical Significance, *Surg, Gynec & Obst* **70** 828 (April) 1940.

varicose veins are associated with or compensatory to deep phlebitis. He presented evidence to show that the elimination of the varicosities in such cases will result in improvement of the associated symptoms of swelling, pain, eczema and ulceration.

Luke asserted that the incompetence of valves in the communicating veins had little scientific proof. He was unable to substantiate their presence by venographic studies. In his opinion, the Trendelenburg "double" reaction was more plausibly explained by incompetence of the small saphenous vein, with filling of the lower veins through the widespread anastomosis known to exist between the two saphenous veins. Clinically this was demonstrated by failure to obtain the "double" reaction when the tourniquet was applied below the knee, thus preventing the backflow of blood from the lesser saphenous vein.

Frykholm⁸³ studied necropsy material, comprising 24 cases of pulmonary embolism, in an attempt to learn the pathogenesis of thrombosis. Sources of beginning thrombosis were noted in the veins of four regions, namely the musculature of the calf of the leg, the adductor musculature and the plantar and pelvic regions. An ascending thrombus seemed to pass from these regions in the direction of the blood stream, while retrograde thrombosis was rare. Early clinical diagnosis of thrombosis requires a thorough examination of these four regions. Veins with thin walls and varicose distention for a greater distance partly collapse during confinement in bed, when intima lies against intima. This occurred particularly in the musculature of the calf of the leg and the adductor muscles, which take the least part in active movements performed in bed and through which minimal amounts of blood pass. In addition there was mechanical pressure. The veins of the soles of the feet and the pelvis can also be assumed to collapse partly under certain conditions. Consequently, since normal metabolism of the intima depends on contact with the circulating blood, when two intima layers are pressed against each other, a disturbance in the nutrition of the endothelium easily occurs. This injury of the vascular endothelium was asserted to be an important primary condition in the origin of thrombosis. Substances given off by the damaged endothelium and by the thrombus promote coagulation, and the thrombus grows in the direction of the blood stream. In stagnant blood a red thrombus, and in quickly flowing blood a white thrombus, develop. The author expressed the belief that in mechanical prophylaxis against thrombosis of the lower limbs the veins of the lower extremities must, at least periodically, be sufficiently distended with blood and the circulation in the threatened region must be sufficiently rapid. Consequently, he advocated raising the head of the

83 Frykholm, R. Pathogenesis of Venous Thrombosis and Mechanical Prophylaxis, *Nord med (Hvgea)* 4 3534 (Dec 2) 1939

bed so high that the patient has the feeling of slipping down and is forced actively to exercise the muscles of the calf of the leg and the adductor group

Barrow⁸⁴ cited an example of fatal pulmonary embolism from superficial phlebitis

Ochsner and DeBakey⁸⁵ asserted that mechanical blockage of the venous and lymphatic systems are not of primary significance in the production of the clinical manifestations in thrombophlebitis. On the basis of recent clinical and experimental investigations they concluded that many of the symptoms and signs were due to vasospasm of the arterial and venous systems and that the vasoconstricting impulses originated in the thrombophlebitic segment. As a result of this vasospasm there occurred increased filtration pressure, relative anoxia of the capillary endothelium and diminution in the flow of lymph, all of which increased the amount of perivascular fluid, resulting in more edema. They stated that interruption of the vasoconstrictor impulses by infiltration of the sympathetic ganglions with procaine hydrochloride resulted in reestablishment of the normal exchange of intravascular and perivascular fluids.

This method was tried clinically in 15 cases involving 17 thrombophlebitic processes. Each patient was treated by procaine block of the sympathetic ganglions. Prompt and permanent relief of all the clinical manifestations resulted, in contrast to the usual production of phlegmasia alba dolens, in which there are pyrexia for from four to six weeks and the likelihood of persistent undesirable sequelae, such as edema, varicosities and ulceration. In half the cases the temperature returned to normal within forty-eight hours, and in the other half within one week. In half the cases the edema completely subsided in eight days, and in the others within twelve days. Sixty per cent of the patients were discharged from the hospital as cured within eight days after the institution of therapy.

Démarez⁸⁶ came to similar conclusions after infiltration of the lumbar sympathetic chain in 3 cases of phlebitis. The pain disappeared, the temperature decreased and edema either did not appear or did not attain the usual importance. The period of hospitalization was not as brief as that in the cases reported by Ochsner and DeBakey, although it was less than usual.

84 Barrow, D W. Fatal Pulmonary Embolism from Superficial Thrombophlebitis, *Ann Surg* **110** 1118 (Dec) 1939

85 Ochsner, A, and DeBakey, M. Thrombophlebitis. Role of Vasospasm in Production of Clinical Manifestations, *J A M A* **114** 117 (Jan 13) 1940

86 Démarez, R. A propos du traitement immédiat des phlébites post-opératoires en chirurgie gynécologique par infiltration du sympathique lombaire, *Bull Soc gynéc et d'obst* **28** 364 (May) 1939

Former reviews have included articles on severe vasospasm complicating thrombophlebitis. Many clinical examples have been cited in which gangrene developed during the course of phlebitis. Some of these were classified under the heading of "venous gangrene." Additional cases have been reported. Gutman⁸⁷ described the case of a 21 year old girl who had postpartum gangrene, probably secondary to thrombophlebitis. Tilley⁸⁸ reported 4 cases of puerperal thrombophlebitis, in 3 of which gangrene, and in 1 a high grade vasospastic disturbance, developed.

EDEMA

Foote, Reed, Comeau and White⁸⁹ analyzed 200 unselected cases of edema of both lower extremities, the predominant causes of the edema and their frequencies were determined. Half these cases (100) were selected from the outpatient department and the other half from the wards of the hospital. In the outpatient group the causative factors occurred in the following order of frequency: varicose veins (56 cases), with obesity (31 cases) and without obesity (25 cases), obesity alone (13 cases), cardiac failure (13 cases), lymphedema (4 cases), renal disease (3 cases), nutritional factors (3 cases), cirrhosis of the liver (2 cases), and miscellaneous factors (6 cases). In the ward groups the causative factors had the following frequency: congestive heart failure (60 cases), varicose veins or obesity alone or in combination (12 cases), renal disease (7 cases), nutritional factors (7 cases), cirrhosis of the liver (7 cases), leukemia (2 cases), myxedema (2 cases) and miscellaneous factors (3 cases). This is an interesting series, particularly since cardiac failure was shown to be far less common as an etiologic factor in bilateral edema of the lower extremities than one would expect in ambulatory patients. Its predominance in ward patients is not unusual, as only those with more severe illness are admitted. From the figures just cited, it is readily seen that in all types of patients varicose veins, with or without obesity, are almost as frequent a cause of edema as cardiac failure.

Allen and Hines⁹⁰ described the clinical syndrome of lipedema. This disorder, which affects women, consists of generalized and sym-

87 Gutman, P. E. Puerperal Gangrene of Extremities, *Am J Obst & Gynec* **36** 154 (July) 1938

88 Tilley, J. H. Gangrene of the Extremities in Puerperal Thrombophlebitis, *Am J Obst & Gynec* **36** 157 (July) 1938

89 Foote, S. A., Jr., Reed, W. C., Comeau, W. J., and White, P. D. The Clinical Significance of Bilateral Edema of the Lower Extremities, *Am J M Sc* **199** 512 (April) 1940

90 Allen, E. V., and Hines, E. A. Vascular Clinics. X Lipedema of the Legs, a Syndrome Characterized by Fat Legs and Orthostatic Edema, *Proc Staff Meet, Mayo Clin* **15** 184 (March 20) 1940

metric fatty swelling of the legs, frequently including the hips. Women with this syndrome showed a tendency to obesity, and the condition was aggravated during standing, particularly in warm weather, when slight pitting might occur. A family history of large legs was obtained in many instances. The edema was soft and did not involve the feet, and pain could be elicited on pressure. The only complaint other than the appearance of the legs was that of aching distress. In no case was there history of recurrent episodes of acute cellulitis, such as may occur in the course of lymphedema. The basic difficulty in this disorder is chiefly an unusual amount of fat beneath the skin, offering abnormally poor resistance to the passage of fluid into the tissues from the blood. Therapy was usually unsatisfactory, reduction in weight and reassurance being helpful.

TREATMENT

This year the trend in the literature on therapy for peripheral vascular diseases is mainly toward the use of drugs. Little mention is made of the mechanical devices previously so popular. Vitamins and estrogenic substances have finally made their appearance, to be included in the vast therapeutic armamentarium for vascular disturbances.

The dangers associated with the use of many ordinary therapeutic procedures for peripheral vascular diseases have been frequently stressed. Oard, Campbell and Dealy,⁹¹ in a study of 40 patients hospitalized because of peripheral vascular diseases, noted that more than half of them sustained one or more types of injury sufficient to produce an open lesion. There were only 13 instances of trauma resulting from self treatment or accident. The remaining 24 instances of trauma occurred through the advice or at the hands of a professional attendant. Usually injury resulted from some form of ill advised therapy in cases in which circulatory failure was not recognized. The authors warned against the use of overheating, excessive pressure, application of strong chemicals and surgical procedures about corns or ingrown toe nails in patients with vascular disturbances, as open lesions develop easily. These lesions were shown to entail great economic loss to the patient, as well as prolonged morbidity and a high death rate.

Pilcher⁹² found that atropine and ephedrine were of little prophylactic value against postoperative thrombosis and pulmonary embolism. He used injections of these drugs routinely in treatment of 406 patients admitted to the hospital because of accident or for operation. Injections were given on the fifth, seventh and ninth days after operation. The

91 Oard, H. C., Campbell, C. R., and Dealy, F. N. Traumatic Complications in Peripheral Vascular Disease, *Am J M Sc* **199** 194 (Feb.) 1940.

92 Pilcher, R. Postoperative Thrombosis and Embolism. Report of Trial of Ephedrine and Atropine as Prophylactic, *Lancet* **1** 752 (April 1) 1939.

incidence of thrombosis and embolism was found to be approximately the same as in a control series of 1,265 cases

Perlow⁹³ reported his results in 31 cases of peripheral circulatory disturbances in which he used prostigmine subcutaneously and orally. As this drug has been shown to produce vasodilatation, it was found most valuable as an adjunct in treating circulatory disturbances in which vasospasm existed. The drug was used clinically in 11 cases of thromboangitis obliterans, 4 of arteriosclerosis, 9 of Raynaud's syndrome, 5 of acrocyanosis and 2 of acute vascular occlusion. Improvement was noted in half the cases, the best results being obtained with thromboangitis obliterans and Raynaud's syndrome. In the cases of thromboangitis claudication improved, and in those of Raynaud's disease the number of daily vasospastic attacks diminished. In 4 of 5 cases of acrocyanosis the drug was found to produce warmth in the hands, but little change in color. An initial subcutaneous injection of 0.5 mg of prostigmine methyl sulfate was given and the degree of vasodilatation noted. During the subsequent week the drug was given by mouth in doses of 7.5 mg of prostigmine bromide three times a day. If no improvement occurred the dose was doubled. In 1 case, 30 mg four times a day was given without success. Amounts up to 60 mg daily were usually tolerated without abdominal cramps. Cessation of action occurred promptly with administration of atropine.

The mechanism of action has been shown by other investigators to be the neutralization of choline esterase, thus permitting the cholinergic substance, normally present, to act at the parasympathetic nerve endings. In the cases of mild primary vasomotor disturbances in the extremities, relief continued as long as prostigmine was administered, with recurrence of symptoms when the drug was stopped.

Weichsel⁹⁴ reported excellent results in patients suffering from intermittent claudication with the intravenous administration of calcium salts. All his 25 patients improved subjectively. Evidence of vasodilatation was noted with the plethysmograph. Calcium gluconate, in doses of 10 to 20 cc of a 10 per cent solution, was originally used, but because of the tediousness of technic, the relative expense and the instability of gluconate, calcium chloride was substituted, with equally good results. The latter drug was administered intravenously by the infusion method in a concentration of 1 or 2 per cent in physiologic solution of sodium chloride. All the patients received 2 Gm of calcium chloride once a week for twelve weeks. Claudication distance (the distance a patient

93 Perlow, S. Prostigmine in the Treatment of Peripheral Circulatory Disturbances, *J A M A* **114** 1991 (May 18) 1940

94 Weichsel, H. S. Studies in Peripheral Vascular Disease. I. Intravenous Calcium in Occlusive Vascular Disease, *Ann Int Med* **13** 1150 (Jan) 1940

could walk before claudication develops) was materially and consistently increased, rest pain and night cramps were reduced and ulcers healed by this form of therapy

Mulinos, Shulman and Mufson⁹⁵ studied the effect of papaverine hydrochloride and histamine iontophoresis in 5 cases of Raynaud's disease. The papaverine was given intravenously in large doses, from 10 to 120 mg, three times a week. The histamine was administered by iontophoresis either before or after the papaverine. Treatment was continuous for from eight to twelve weeks and was terminated by the advent of warm weather. After prolonged treatment the blood flow to the hand increased 33 per cent, and the average hand capacity increased 47 per cent over the preinjection levels. After injection of papaverine, histamine usually decreased the rate of inflow but increased further the capacity of the hand. With the simple plethysmographic method, papaverine was shown to increase the volume of the hand from 5 to an average of 13.8 cc. A further increase was noted when papaverine was given after histamine iontophoresis. The cutaneous temperature increased after the injection of papaverine. No changes in oscillometric readings were noted during a period of forty-five minutes after injection. Cutaneous temperature was decreased after histamine iontophoresis, but this was always elevated after the administration of papaverine. Capillary microscopy revealed an increase in speed of blood flow after injection of papaverine, but histamine not uncommonly lessened the flow.

Clinically, the patients improved under this regimen. Exposure to cold no longer produced syncope, cyanosis and pain in the extremities. Despite the long-continued treatment, little cerebral depression occurred, and no one became addicted to the drug.

Fisher, Duryee and Wright⁹⁶ studied the effect of a deproteinized tissue extract on patients suffering from intermittent claudication due to arteriosclerosis obliterans. In so doing, a new apparatus to measure claudication time was described. This consisted of a vertical stand fitted with a foot pedal which, when depressed, raised a weight of 13.6 pounds (6.2 Kg). The claudication time thus depended on the length of time a given subject was able to use this apparatus at a constant rate of speed. Improvement of claudication time was noted in 23 of a series of 27 patients after the injection of deproteinized tissue extract. This response was as a rule temporary, as after ten or more injections only 19 patients showed improvement, however, the claudication time

95 Mulinos, M. G., Shulman, I., and Mufson, I. On the Treatment of Raynaud's Disease with Papaverine Intravenously, *Am J M Sc* **197** 793 (June) 1939

96 Fisher, M. M., Duryee, A. W., and Wright, I. S. Deproteinized Pancreatic Extract (Depropanex). I. Effect in the Treatment of Intermittent Claudication Due to Arteriosclerosis Obliterans, *Am Heart J* **18** 425 (Oct.) 1939

in this series was prolonged to an average of more than three times that of the control subject. Physiologic solution of sodium chloride substituted for the extract failed to produce an increase in claudication time under identical conditions.

Meleney⁹⁷ stressed the importance of bacteriologic studies of the involved areas in cases of diabetic gangrene. Although the infected areas usually contain a mixture of organisms, aerobic and anaerobic cultures should be taken as an aid to surgical judgment, as well as a guide to specific therapy against the predominant organism. Meleney stated that zinc peroxide markedly inhibits the growth of the hemolytic streptococci and all anaerobic bacteria, including the organisms causing gas gangrene and anaerobic streptococci. It neutralizes or inactivates the toxins formed by these organisms and at the same time encourages the reparative process by the stimulation of granulation tissue. Zinc peroxide, which is a white powder, should be suspended in sterile distilled water and applied to every part of the surface of the wound. The author found this drug an effective antiseptic to minimize the possibility of the establishment of infection at the time of the primary injury and a means of continuing surface protection. If hemolytic streptococci and anaerobic organisms are present at the site of amputation, zinc peroxide is advised as a prophylactic to prevent the development of infection in the stump, or if infection has developed the drug should be used as early as possible to control it.

Herrmann and McGrath,⁹⁸ in the treatment of 16 patients with arterial insufficiency due to secondary vasomotor instability, associated with active arteritis or phlebitis, used moderate quantities of estrogen parenterally (estrone, or theelin) at regular intervals for at least sixteen weeks. The final evaluation of the patient's condition was based on objective studies of the efficiency of the peripheral vascular system and on an analysis of the patient's account of the effects on the signs and symptoms of the disease of a variety of environmental conditions. Twelve patients who had pronounced pain were given moderately large amounts (50 mg intravenously each day for five days) of thiamine chloride, in addition to the estrogenic substances. Eleven of the 16 patients were so much improved that they were able to return to their work. Either the vasomotor instability completely disappeared or the disease process remained so quiescent that it caused no great disability or concern. Pain in the digits showed equal improvement. Vascular studies on these patients showed a more nearly normal response of the blood vessels

97 Meleney, F. L. The Use of Zinc Peroxide in the Treatment of Diabetic Gangrene of the Lower Extremities, *Surgery* 6:845 (Dec.) 1939.

98 Herrmann, L. G., and McGrath, E. J. Effect of Estrogens on Vascular Spasm Due to Active Anguitis in the Extremities, *Arch. Surg.* 40:334 (Feb.) 1940.

under natural environmental conditions and in a room at constant temperature. Three patients had a recurrence of the signs and symptoms after two years of relief, but the activity of the process again subsided, though less completely, after another course of treatment with estrogen. The symptoms of 4 of the remaining patients have remained unchanged after many months of observation, and those of the last patient have continued to grow worse, in spite of all therapeutic effort.

Edwards, Hamilton and Duntley⁹⁹ made a preliminary report on the effect of crystalline testosterone propionate in the treatment of 7 male patients suffering from organic vascular disease. Three of the men presented typical signs of thromboangitis obliterans, and the other 4 were arteriosclerotic. In all 7 patients the involvement was major, with loss of the popliteal, the femoral and, in 1 case, the iliac pulsations. The signs and symptoms were marked, including small ulcerations in 2 of the patients with thromboangitis obliterans. The testosterone propionate, dissolved in peanut oil, was given intramuscularly two or three times a week. Adjunctive treatment consisted only of general hygiene, except in the case of the ulcer-free patient with thromboangitis obliterans, who received eight hours of suction pressure treatment. None of the patients was followed for more than several months. In each of the patients spectrophotometric examination showed lack of arterIALIZATION of the skin, which involved not only the diseased limbs but also the entire body. Administration of testosterone propionate produced an early and decided arterIALIZATION of the cutaneous blood. Moreover, the after-treatment curves likewise showed an inconstant diminution in the volume of blood in the more venous areas of the body. Other objective evidence of favorable change was an increase in the systolic pressure of from 6 to 26 mm of mercury in the hypotensive members of this group and lowering of the pressure in 2 patients with hypertension. The ulceration in 1 patient with thromboangitis obliterans was healed, in the second it was greatly improved. There was marked improvement in the walking ability of all the patients, with delay or abolition of intermittent claudication. Two patients were no longer subject to night pain. Subjectively, the patients reported increased activity and a feeling of optimism, results similar to those reported previously with this treatment.

Ochsner and Smith¹⁰⁰ were able to control the pain of varicose ulcers with rather large doses of vitamin B₁, thus confirming the recent work

99 Edwards, E. A., Hamilton, J. B., and Duntley, S. Q. Testosterone Propionate as Therapeutic Agent in Patients with Organic Disease of Peripheral Vessels. Preliminary Report, *New England J. Med.* **220**: 865 (May 25) 1939.

100 Ochsner, A., and Smith, M. C. The Use of Vitamin B₁ for the Relief of Pain in Varicose Ulcers, *J. A. M. A.* **114**: 947 (March 16) 1940.

of European investigators. The dose suggested was 5 mg three times a day, to be doubled within three or four days if relief from symptoms did not occur. Ten patients received this vitamin, in the form of thiamine chloride, orally. Within an average of five days complete relief was obtained. In 5 of the 10 patients there was, in addition to the relief of symptoms, definite improvement in the healing of the ulcer, even though the condition had been resistant to therapy prior to vitamin administration. No explanation for the rationale of this therapy was given, except that the patients possibly were deficient in vitamin B₁.

The value of synthetic vitamin B₁ in treatment of painful amputated stumps was reported by Shosberg¹⁰¹. It is discussed in the surgical review.

The value of heparin in vascular diseases is also considered in the surgical section of this review. Mention, however, will be made at this time of its value in thrombophlebitis, as described by Murray¹⁰². He found it of value in the treatment of this disease as it prevented further extension of thrombosis and allowed healing to take place.

Articles favorable to the revival of Buerger's exercises are worthy of mention. These exercises consist either of activity performed by the patient, as originally described, or of passive movement with the oscillating bed.

Kaiser¹⁰³ was able to improve the circulation in the distal portion of the extremities in 19 cases of peripheral vascular disease associated with diabetes with Buerger's exercises as the sole form of treatment. The exercises described vary but little from the original save in time limits, those of each, particularly the rest period, being slightly extended. As an example, the dependent portion was maintained for one minute longer than was necessary for complete rubor to occur, usually from two to five minutes. The rest periods in the horizontal position lasted five minutes. Each cycle lasted about ten minutes, and the patient started with three cycles three times a day, increasing one cycle per day until every other waking hour was devoted to exercises. With this regimen alone 4 of 5 patients with ulcers only were improved, and 11 of 14 without ulcers but with vascular symptoms had relief. Most of the failures were found among uncooperative patients or those with complications. No mention was made of whether the patient was ambulatory or confined to bed.

101 Shosberg, R. Le traitement des algies des amputés par la vitamine B synthétique, *Presse med* **47** 1585 (Dec 6-9) 1939.

102 Murray, G. (a) Heparin in Surgical Treatment of Blood Vessels, *Arch Surg* **40** 307 (Feb) 1940, (b) Heparin in Thrombosis and Embolism, *Brit J Surg* **27** 567 (Jan) 1940.

103 Kaiser, H. L. Buerger's Exercises for Diabetic Patients with Peripheral Vascular Diseases, *Physiotherapy Rev* **20** 18 (Jan-Feb) 1940.

Barker¹⁰⁴ found the oscillating bed to be a valuable adjunct to therapy in 85 cases of peripheral occlusive disease. The physiologic effects noted were (1) definite rhythmic changes in color of the feet and toes, namely, pallor when elevated and rubor when dependent, indicating alternate emptying and filling of the capillary bed, (2) rather striking and rapid relief of pain of vascular origin in a large number of cases during the time that the patient was in the bed, (3) induction of sleep in a large number of cases, even when the patient had had great difficulty in sleeping for some time, and (4) definite but complete vasodilatation, as evidenced by a rise in the cutaneous temperature of the digits. Patients with intermittent claudication received little or no benefit. Of 13 patients with so-called rest, or pretiophic, pain, without ulceration or gangrene, 12 obtained relief during treatment, but it was maintained only in 11 of these patients after treatments were discontinued. Complete and sustained relief of pain was obtained in 9 of 15 patients with ischemic neuritis.

Of the 44 patients with ulceration, gangrene and severe pain, 32 received relief of pain while in the bed, but only 22 maintained this improvement after treatment was discontinued. In these 22 cases the gangrene and ulcerative lesions healed. Specific treatment, with the oscillating bed, was used in some of these cases. Barker expressed the opinion that the oscillating bed is a valuable addition to the armamentarium in the treatment of peripheral vascular disease but should not supplant the other methods now used, as it can be readily used in conjunction with them.

Kramer¹⁰⁵ treated a series of 103 patients with intermittent venous occlusion. In all, about 1,500 treatments were given. The results in the group with Buerger's disease and arteriosclerosis with diabetes were average, 66.6 per cent of patients being benefited. The results in the group with arteriosclerosis without diabetes were disappointing, being favorable in 60 per cent. The largest series consisted of 33 patients with phlebitis. In these patients symptoms were due mainly to reflex vasospasm and were favorably influenced in 72.8 per cent. The results of this type of therapy were evaluated through improvement in symptoms. Eighty-five per cent of the patients obtained relief from fatigue, 77 per cent from cramps and 71 per cent from pain. In the entire series, 70 patients were thought to be benefited.

104 Barker, N. W. The Use of Oscillating Beds in the Treatment of Peripheral Occlusive Arterial Disease, *Proc. Staff Meet., Mayo Clin.* **14**: 618 (Sept. 27) 1939.

105 Kramer, D. W. Intermittent Venous Compression in the Treatment of Peripheral Vascular Disorders, *Am. J. M. Sc.* **197**: 808 (June) 1939.

ARTERIAL HYPERTENSION

The committees¹⁰⁶ for the standardization of blood pressure readings of the American Heart Association and the Cardiac Society of Great Britain and Ireland have recommended a standard procedure for the measurement of arterial blood pressure. The need for a definite procedure is obvious, as wide variations in technic and interpretation have been noted among different groups of physicians, teachers and life insurance examiners and students.

Especially to be noted are the preparation and position of the patient and the method of application of the cuff. Lack of care in these fundamentals often results in conspicuous errors. Likewise, the proper care and inspection of the apparatus for sources of error are of utmost importance. The possibilities of error due to faulty equipment are great.

The patient should be lying or sitting comfortably and relaxed. The cuff, completely deflated, should be applied to the inner side of the arm, snugly and evenly, with the lower edge about 1 inch (2.5 cm) above the antecubital space. The cuff should be applied smoothly and in such a way that neither bulging nor displacement occurs. It is recommended that palpation be used as a check on the auscultatory readings. The pressure should be raised in steps of 10 mm of mercury until the radial pulse ceases and then be allowed to fall rapidly. The higher of the two readings, palpatory or auscultatory, should be accepted as the systolic pressure. The bell of the stethoscope should be applied over the previously palpated brachial artery in the antecubital space with a minimum of pressure to secure complete apposition to the skin. The pressure in the cuff should be raised about 30 mm of mercury above the level at which the radial artery can be felt and then deflated at the rate of 2 to 3 mm per second. The level at which the first sound appears is to be considered the systolic pressure unless the palpatory level is higher. As the cuff is still further deflated, the point at which the sounds suddenly become muffled should be considered the diastolic pressure. If this point and that at which the sounds entirely disappear are not the same, the American committee recommends that the latter also be considered as the diastolic pressure and that both readings be recorded. This may be expressed as 140/80-70 or 140/70-0. The cuff should be completely deflated before any other readings are made.

106 Standard Method for Taking and Recording Blood Pressure Readings, by Committee for the Standardization of Blood Pressure Readings of the American Heart Association and the Committee for the Standardization of Blood Pressure Readings of the Cardiac Society of Great Britain and Ireland, *J A M A* **113** 294 (July 22) 1939

Physical and psychologic factors are to be considered. The relation to blood pressure readings of exercise, intake of food, emotional state of the patient and time of day is important. The possibility of variations in the two arms should be remembered. In the presence of cardiac arrhythmias blood pressure readings are inaccurate at best. Extrasystoles in which the systolic pressure is higher than average should not be considered as the systolic pressure. With auricular fibrillation, it is suggested that an average of several readings is necessary even to approximate a blood pressure reading.

Further suggestions are made in the report of the committees. This report should be read in its original form by all students.

Robinson and Brucer¹⁰⁷ made a statistical study of a very large group of persons in an attempt to establish a more accurate notion of what constitutes normal blood pressure. They are somewhat caustic in their comment on the opinions of other observers, and in some respects are probably on the right path. At any rate, the study is an extensive one, and well done, and deserves consideration and thought. The authors concluded that the normal range of the systolic blood pressure is from 90 to 120 mm of mercury and that of the diastolic from 60 to 80 mm. Almost two thirds of all blood pressure readings for the total group were below 125 systolic and 80 diastolic.

They pointed out that there is no such disease entity as hypertension and that in the absence of other findings, which should be carefully ruled out, a low pressure is an ideal blood pressure. With this view there can be but little disagreement. The fallacy concerning the rise in blood pressure with age was also emphasized. Prehypertensive blood pressures, as well as definite hypertensive pressures, do increase with age. The blood pressure of the normal person becomes more or less stabilized at adolescence and remains fairly constant throughout life. The lower the average blood pressure level, the less variation in pressure is noted. Pressures below 120 mm of mercury systolic are less variable and erratic than pressures above 120 mm. Pressures below this level are more likely to retain a constant level, while those above tend to increase with age. The authors stated that the upper limit of normal for systolic pressure is 120 mm of mercury.

This raises the question of what significance is to be attached to pressures slightly higher than normal. Certainly they should not be considered as indicative of hypertension. There are many conditions in which a slight rise of blood pressure is symptomatic. It should also be remembered that such figures as have been arrived at by the authors

¹⁰⁷ Robinson, S. C., and Brucer, M. Range of Normal Blood Pressure. A Statistical and Clinical Study of 11,383 Persons, *Arch Int Med* **64**: 409 (Sept) 1939.

indicate a general trend and cannot be applied directly to each person as an inflexible rule. There are no doubt many exceptions, although the statement is made that the history of a blood pressure of over 120 systolic and 80 diastolic for a ten year span "is almost an infallible sign of incipient hypertension."

The authors stated "Slightly more than 40 per cent of the adult population is either actually or incipiently hypertensive." If the author's conclusions in this respect are to be accepted, the number of persons who must be regarded as hypertensive will be tremendously increased, and 40 per cent seems a conservative figure. A second question arises. What is meant by the authors' term "incipient hypertension"? In the conclusions no mention is made of the etiologic factors involved in increased blood pressure or of the various patterns.

It is true that this work is provocative, from its nature, it is important that further similar studies be made. A defect in this paper is the consideration of blood pressure readings without regard to the cause of increased pressure. It is the analysis of a single symptom treated as an entity.

Schroeder and Steele¹⁰⁸ have attempted to classify a group of cases of essential hypertension according to the significant phenomena presented in each case. The purpose is apparently to suggest an etiologic relationship. They grouped these cases on the basis of disturbances in the renal, nervous, endocrine and vascular symptoms. There was a fifth group which could not be classified. They regarded as suggestive the fact that hypertension can be produced experimentally in animals by disturbing one or the other of at least three of the four systems.

The first group included cases of glomerulonephritis, pyelonephritis, bilateral hydronephrosis, persistent polyuria and other renal abnormalities. In the second group, of the symptoms related to the central nervous system which were encountered, the diencephalic syndrome accounted for a fair portion of the cases. Vasomotor instability, autonomic instability and endocrine factors were present in several of the other cases. Symptoms of this type were usually found in young women, in a few instances in older women and only occasionally in men. Significant changes in the eyegrounds were rare in this group. Evidence of some endocrine disturbance was present in 41 women and 2 men of the third group. Basal metabolic rates were elevated in the absence of obvious goiter in some patients, while others were definitely thyrotoxic at the onset of the hypertension. In 9 of this group, the onset of the increase in blood pressure occurred at the menopause. Obesity and hypertrichosis were also manifestations. Cushing's syndrome was present in 3 of the endocrine group.

108 Schroeder, H. A., and Steele, J. M. Studies on "Essential" Hypertension I. Classification, *Arch Int Med* 64:927 (Nov.) 1939.

Arteriosclerosis was the most common factor, other than hypertension. In the unclassified group were those cases in which hypertension began during pregnancy and the cases of malignant hypertension. The significance of this grouping is uncertain.

Williams and Harrison¹⁰⁹ also attempted to classify hypertension under various syndromes according to the probable underlying and aggravating causes. This could not be done with certainty, but in most cases they found one or more factors which seemed to offer opportunity for the alleviation of symptoms at least. Group 1 represented cases of neurogenic origin, group 2, cases of endocrine disturbance, group 3, cases of renal hypertension, including acute and chronic nephritis, urinary obstruction, disease of the renal arteries and tumors, group 4, cases of metabolic hypertension and hypercholesteremia with renal atheroma and gout, group 5, cases of hypertension caused by congestive heart failure (which is open to question), and group 6, unclassified cases.

Many of the conditions which have been listed seem to produce hypertension only when they occur in predisposed subjects.

Ivy and McEwen¹¹⁰ discussed in outline form some of the physiologic aspects of hypertension. Both increased peripheral resistance in the arteriolar bed and loss of elasticity in the larger arteries are probably essential factors in clinical hypertension. These factors in an artificial circulation experiment resulted in variations in pressure similar to those found in clinical hypertension. The authors asserted that the essential factors in experimental hypertension were produced by renal ischemia. They expressed the belief that ischemia of other abdominal viscera is not a factor and that the nervous system is not involved in the Goldblatt type of hypertension. Of the endocrine glands, only the adrenal cortex is necessary for the manifestation of increased blood pressure. There is at least presumptive evidence that the hypertension is due to a humoral agent of renal origin and that hypertension of both the so-called benign and the malignant type can be produced in Goldblatt animals. The question of the nature of the probable pressor substance was considered. That it is an intermediate product of an enzyme acting on a substrate present in the blood seems possible. Another alternative is that the renal hypertensive substance is not a vasoconstrictor per se but acts in conjunction with other hormones or substances. It is also possible that the renal substance may neutralize some

109 Williams, J. R., Jr., and Harrison, T. R. Clinical Pictures Associated with Increased Blood Pressure. A Study of One Hundred Patients, *Ann Int Med* **13** 650 (Oct.) 1939.

110 Ivy, A. C., and McEwen, E. G. A Physiological Consideration of Certain Aspects of Hypertension, *Quart Bull Northwestern Univ M School* **14** 72, 1940.

depressor substance normally present in the blood, or that it may be an arteriolar toxin which gradually causes degenerative changes in the arteriolar wall

That renin is inactive as a vasoconstrictor substance except in the presence of whole blood, plasma or erythrocyte protein was shown by the continued experiments of Page and his associates¹¹¹ This activating substance is thermolabile It is also present in increased amounts in the plasma of dogs with experimental hypertension

Rodbard and Katz¹¹² conducted experiments on dogs which indicated that the renal pressor substance was rapidly excreted, lost or destroyed when the ischemic kidney was removed and a normal kidney remained, but if the normal kidney had been previously removed the increased blood pressure was found to endure about five times as long Normal blood pressure has no relation to the kidney, but "renal hypertension depends upon the kidney for its genesis, continuation and elimination"

With this view Williams, Diaz, Burch and Harrison¹¹³ expressed essential agreement—that is, that renin plays no role in regulating normal blood pressure They also found in their experiments on rats that the hypertension in hypophysectomized animals is not related to the renal pressor substance, or that if such a relationship exists it must be mediated through some unknown mechanism They found no relation between the gonads and blood pressure

The animals which were adrenalectomized showed a fall in blood pressure, although they were kept alive by means of the administration of a solution of sodium chloride They were markedly less sensitive to renin than were normal animals The kidneys of these animals contained as much renin as did those of normal animals by the methods of assay used by the authors The same was found to be true in the hypophysectomized animals

Stead and Kunkel¹¹⁴ noted that in normal human subjects paredrinol produces a type of hypertension resembling closely that observed in disease The average duration after intramuscular injection of 25 mg of the drug is one hour In addition to hypertension, there are slowing of the heart rate, increased vigor of the apex impulse and appearance of

111 Kohlstaedt, K G , Page, I H , and Helmar, O M The Activation of Renin by Blood, *Am Heart J* **19** 92 (Jan) 1940

112 Rodbard, S , and Katz, L N Elimination of the Effect of the Chemical Mediator of Renal Hypertension, *Ann J M Sc* **198** 602 (Nov) 1939

113 Williams, J R , Jr , Diaz, J T , Burch, J C , and Harrison, T R The Relation of the Adrenal Glands to the Action of the Renal Pressor Substance, *Am J M Sc* **198** 212 (Aug) 1939

114 Stead, E A , Jr , and Kunkel, P Mechanism of the Arterial Hypertension Produced by Paredrinol, *J Clin Investigation* **18** 439 (July) 1939

loud heart tones. The effect is not always constant. The rate of blood flow in the dilated hand is moderately decreased, as are the fluctuations in vasomotor tone in the hand and foot. A rise in venous pressure occurs, and the T waves of the electrocardiogram are increased. The cardiac output, circulation time and basal metabolism are not significantly altered.

The decrease in heart rate is an effect of the vagus nerve resulting from stimulation of the carotid sinus and aortic nerves. This can be removed by the administration of atropine. When atropine is given, the heart rate is increased and the blood pressure, particularly the diastolic, rises to higher levels. The rise in pressure can be controlled by the use of nitrites and by placing the patient in the upright position. The authors expressed the opinion that both a direct vasoconstrictor effect on the peripheral vascular bed and an increase in venous tone are factors.

Iglauer and Altschule¹¹⁵ concluded that both benzedrine and paredrine cause a rise in blood pressure by increased arteriolar vasoconstriction. They found that the pressor effects persist after the paralysis of the vasomotor nerves which occurs with spinal anesthesia. In their opinion, the evidence indicates that the smooth muscle of the arterioles is the site of action of these drugs.

Taquini¹¹⁶ demonstrated the presence of a pressor substance produced by the totally ischemic kidney if the occlusion of the renal pedicle is temporary. This work was done on dogs, and the results were fairly uniform. After establishment of the circulation, a rise in blood pressure took place. Taquini concluded that the rise in pressure which occurs under these conditions is the result of the elaboration of a substance found during the period of total ischemia. This substance acts directly on the peripheral vessels, and hypertension is produced by the peripheral vasoconstriction which is induced by this direct action of this substance on the walls of the blood vessels.

Major and his associates¹¹⁷ reported on continuation of their work on "blood guanidine." They found an increase of this substance in the blood of animals in which arteriovenous fistula of the renal arteries and veins was created. This increase in "guanidine" was found in animals with experimental renal insufficiency both with and without accompanying hypertension. The exact chemical nature of this "guanidine-like substance" is still not definitely determined.

115 Iglauer, A, and Altschule M. D. The Pressor Action of Benzedrine and Paredrine, *Am J M Sc* **199** 359 (March) 1940

116 Taquini A. C. The Production of Pressor Substance by the Totally Ischemic Kidney. *Am Heart J* **19** 513 (May) 1940

117 Major, R. H. Weber, C. J. and Rumold J. J. Blood "Guanidine." Further Observations. *Arch Int Med* **64** 988 (Nov) 1939

In an attempt to evaluate the cold pressor test, Thomas and Warthin¹¹⁸ subjected dogs, both those with normal pressures and those in which hypertension had been induced, to a standard cold stimulus. In the normal dogs there was no response which could be interpreted as a pressor reaction, although some showed a rise in blood pressure, which tended to diminish as the animals became trained to the procedure. In 87 per cent of the group with renal hypertension the results of the tests were reported as negative. In the animals in which hypertension was induced by buffer nerve section the reaction to the cold test was variable, more often negative than positive. In none of the animals was there a reaction analogous to that in man. The authors concluded that experimental hypertension in dogs produced by renal ischemia is more nearly analogous to the hypertension of renal disease in man than to essential hypertension. Physiologically this seems probable and is in agreement with the results of Miller and Bruger,¹¹⁹ who made cold pressor observations on normal persons and on those with renal hypertension, as well as on patients with essential hypertension. They found that the patients with chronic nephritis gave a response similar to that of normal subjects who did not show hyperreactions. There was a slight rise in blood pressure above that of normal persons in this group. Thirty-nine per cent of the normal group gave hyperreactions, and 76 per cent of the group with essential hypertension had a significant rise in pressure in response to the test. Among the older patients with essential hypertension, in whom arteriosclerosis, albuminuria and other evidences of renal disease were present, the pressor response was not as marked as in the younger members of this group.

Hines,¹²⁰ in a discussion of the significance of vascular hyperreaction as measured by the cold pressor test, stressed again the technic of the procedure. It is generally conceded that quick rises in blood pressure unassociated with increase in heart rate or cardiac output are the result of increased peripheral resistance, which in turn is the result of vasoconstriction in the arteriolar bed. The rise in blood pressure following the cold pressor test may be regarded as an index of vascular reactivity. It is pointed out that, as in all clinical tests, there is a certain amount of normal individual variation, but that if care is taken to secure the same basal conditions and to follow the same technic, essentially the same response is elicited in the same subject in repeated tests. Varia-

118 Thomas, C. B., and Warthin, T. A. The Response of Normal Dogs and Dogs with Experimental Hypertension to a Standard Cold Stimulus, *Am Heart J* **19** 316 (March) 1940.

119 Miller, J. H., and Bruger, M. The Cold Pressor Test in Normal Subjects and Patients with Primary (Essential) and Secondary (Renal) Hypertension, *Am Heart J* **18** 329 (Sept.) 1939.

120 Hines, E. A., Jr. The Significance of the Vascular Hyperreaction as Measured by the Cold Pressor Test, *Am Heart J* **19** 408 (April) 1940.

tions in the response to the test resulting in discrepancies of interpretation can be explained, according to Hines, by variations in the technic of the test. The diastolic response to the stimulus is regarded as a more reliable index of vasoconstriction than the systolic. Both systolic and diastolic rises should be considered in evaluating the result. A significant response was regarded by Hines to be a rise of more than 20 mm of mercury systolic and of more than 15 mm diastolic. Such an increase above the basal level would indicate a hyperreactive vasoconstrictor mechanism.

Of persons whose blood pressure was usually normal, Hines found a mean systolic rise in the older age group. The mean diastolic response of children with normal blood pressure was increased, but that of persons more than 50 years of age was decreased. Persons with essential hypertension showed a mean diastolic response which was about the same at all ages.

The response of persons with hypertension was from two to six times as great as that of persons whose blood pressure was usually normal, and in some subjects it was extreme. It has been found that in patients in whom hypertension is developing the response is unusually marked. Hines expressed the belief that this hyperactivity is an important etiologic factor in essential hypertension.

A significant increase in the response was found in a group of persons who were known to have had hypertension in the past but whose blood pressure was normal at the time of the test. The same was true of persons who showed signs of hypertension in the fundi but whose blood pressure was usually normal. These persons were regarded as having latent hypertension. It appears from the work of Hines and others that vasoconstrictor hyperreaction may be regarded as an inherited characteristic. There appears to be a correlation between a hyperreactor response to the cold pressor test and the increased response to nervous or psychic stress, such as is sometimes noted in an initial blood pressure reading, which is commonly found to be higher than the average recorded subsequently.

Stead and Kunkel¹²¹ found a uniform increase in peripheral resistance in all parts of the body. It could not be reduced to normal in the skin of the extremities, in the muscles of the forearm or in the brain by vasodilating stimuli. Measurement of the blood flow in the foot of a person with essential hypertension showed no change after malaria, although a marked fall in arterial pressure occurred. This was interpreted to mean that there had been no structural change in the vessels. Another patient observed under similar conditions showed a decrease in blood flow with the fall in arterial blood pressure. This

121 Stead, E. J., Jr., and Kunkel, P. The Nature of Peripheral Resistance in Arterial Hypertension, *J Clin Investigation* 19:25 (Jan) 1940.

was interpreted as indicating extensive structural alteration in the vessel wall, although vasoconstriction was probably the initial factor responsible for hypertension

Vasoconstrictor responses to sensory stimuli remained the same in spite of the fall in blood pressure with malaria. This identical response was found also in some normal subjects, as well as in persons with essential hypertension.

Engle and Binger¹²² made observations on the effect on blood pressure of acetylbetamethylcholine in persons with hypertension and in normal persons. Their findings support the hypothesis that a deficient acetylcholine vasodilator mechanism may be a factor at least in some types of arterial hypertension. In support of this view, a definitely greater percentage decrease in blood pressure was found in persons with essential hypertension than in normal persons. The dose of the drug, injected subcutaneously, was 2.5 mg. Little or no change was noted in normal persons, while in patients with hypertension a well marked fall occurred, amounting to three or four times that of normal subjects. A rise in heart rate corresponding to the fall in blood pressure was noted. This occurred in all types of hypertension.

When the cold pressor test was applied after administration of the drug it was found that the vasoconstrictor response was markedly decreased. Conversely, there was a more marked fall in blood pressure with this drug than was observed during anesthesia induced by the intravenous injection of pentothal sodium (sodium ethyl 1-methylbutylthiobarbiturate).

It is interesting to note that dogs in which hypertension had been induced by renal ischemia showed no greater fall in blood pressure after the drug was administered than did normal dogs. This illustrates another point in which experimental renal hypertension differs from essential hypertension in man.

It is curious that persons with the hypertension of chronic glomerulonephritis should show nearly as marked a fall in pressure in response to the injection of acetylbetamethylcholine as do persons with essential hypertension.

The reaction seems to be peculiar to hypertension. A small group of subjects were tested in whom there had previously been a fall in blood pressure from a hypertensive to a normal level. These subjects showed a much greater response to the drug than did normal persons.

It would seem that this approach to the problem of hypertension is important and that it deserves much more consideration, as the authors have stated in conclusion.

122 Engle, D. E., and Binger, M. W. The Response in Blood Pressure of Hypertensive Patients to Acetyl-Beta-Methylcholine, *Am J M Sc* **198** 609 (Nov.) 1939.

Wagener and Keith,¹²³ in an excellent discussion of the problem of hypertension, arteriolar disease and the associated retinal lesions, have led one to believe that regardless of the original initiating factor, whether inflammatory renal disease or functional arteriolar spasm, persistent hypertension is probably of renal origin. Anatomic lesions in the arterioles of the kidneys seem to be the primary site of origin of the hypertension syndrome. In the more rapidly progressive form lesions are present in the endothelium. The authors suggested that such changes may be the result of spasm, persistent and severe, in these vessels. When this occurs the picture which they have termed malignant hypertension is present. They repeated their classification of the hypertension syndrome under four types, using the same basis as they had previously employed. The differentiation seems somewhat clearer and better defined in the light of more recent knowledge.

However, the underlying, and perhaps the most important, idea advanced is that hypertension may result from primary renal disease, as well as when no primary or secondary lesion of the kidneys is present. The rise in blood pressure may be acute and of short duration in both types. When this is true the tendency is for the blood pressure to return to normal. When the blood pressure remains elevated in cases of chronic glomerulonephritis, diffuse lesions of the arterioles can be shown both in the retina and in other structures. In all cases included in the study diffuse vascular lesions of these types were present. There was no relation to the size or the functional capacity of the kidneys.

Unilateral pyelonephritis with advanced vascular lesions may or may not be associated with hypertension. The authors stated that because the vascular lesions in pyelonephritis are similar to those in malignant nephrosclerosis there is a tendency for the hypertension in pyelonephritis, when it does occur, to be severe. In fact, they stated that pyelonephritis is responsible for 15 to 20 per cent of the cases of malignant hypertension. The vascular lesions in this disease are restricted to the kidneys, in contrast to those seen in the vascular type of malignant hypertension, in which the disease process is diffuse.

The importance of diffuse arteriolar disease is again emphasized. It results in hypertension of the Goldblatt type and is often amenable to treatment. It was said by the authors to be more common than chronic glomerulonephritis.

Schroeder and Fish¹²⁴ reported on 7 patients with arterial hypertension who had associated unilateral organic disease of the kidneys.

123 Wagener, H. P., and Keith, N. M. Diffuse Arteriolar Disease with Hypertension and the Associated Retinal Lesions, *Medicine* **18** 317 (Sept.) 1939.

124 Schroeder, H. A., and Fish, G. W. Studies on "Essential" Hypertension. III. Effect of Nephrectomy upon Hypertension Associated with Organic Renal Disease, *Am. J. M. Sc.* **199** 601 (May) 1940.

These patients were subjected to nephrectomy. Two improved remarkably and 2 slightly, the rest did not improve. The authors stated that if nephrectomy is to be of definite benefit in such cases the hypertension must have been of short duration and the arteriolar sclerosis of the other kidney in an early stage. This seems to be an important observation.

Dicker,¹²⁵ from the observation and careful study of 2 patients, concluded that for the kidneys to cause hypertension the renal circulation must be constricted. All the other renal and urinary manifestations are secondary and play no part in the hypertension, even though fatal renal insufficiency may exist.

Goldbloom and Lieberman¹²⁶ reported 3 cases of malignant nephrosclerosis proved at autopsy in which during life examination of the fundi failed to show any evidence of edema of the optic disk, although the other signs of angiospastic retinopathy were present. Such observations are probably not as uncommon as has been generally thought.

Kvale, Allen and Adson¹²⁷ reported studies on the circulation time in persons with hypertension. They found it essentially the same as in normal subjects except that the "arm to foot" time was slightly increased. They suggested that there might be some diminution of blood flow to the feet in essential hypertension.

Rosenberg¹²⁸ made a careful study of the brains of 17 persons whose death was caused by the phenomena of malignant hypertension. It is important to note that transient cerebral phenomena have been often designated by such terms as cerebral vascular crises and hypertensive encephalopathy. In this group of cases these symptoms were associated with widespread pathologic lesions within the brain. Such transient phenomena have frequently been considered to be caused by arterial or arteriolar spasm. Rosenberg again called attention to the fact that such phenomena are probably based on organic vascular defects. He found that there were three main types of cerebral symptoms in this group of cases: (1) those of increased intracranial pressure, (2) those resulting from multiple miliary cerebral lesions and (3) those of large vascular accidents. Combinations of these types constitute a fourth group. Increased intracranial pressure usually results

125 Dicker, E. The Role of the Kidney in the Reduction of Arterial Hypertension, *Am J M Sc* **199** 616 (May) 1940.

126 Goldbloom, A. A., and Lieberman, A. Renal Arteriolonecrosis Without Papilledema, *Am J M Sc* **198** 52 (July) 1939.

127 Kvale, W. F., Allen, E. A., and Adson, A. W. The Rate of Circulation in the Arteries and Veins of Man. II. Studies of Hypertension and Orthostatic Hypotension and the Effects of Sympathectomy, *Am Heart J* **18** 537 (Nov.) 1939.

128 Rosenberg, E. F. The Brain in Malignant Hypertension. A Clinicopathologic Study, *Arch Int Med* **65** 545 (March) 1940.

from intracerebral or extracerebral edema. The symptoms noted were severe headaches, nausea and vomiting, mental dulness and drowsiness. The symptoms due to multiple destructive miliary lesions were widespread and of varying nature, depending on the portion of the brain involved. Transient hemiplegia and paraplegia, personality changes, fatigue and olfactory hallucinations were among those noted. In the event of extensive cerebral vascular accidents the expected symptoms were found. In all cases the cerebral arterioles were markedly altered. There were an increase in the thickness of the wall and reduction in the caliber of the lumen.

Master, Dack and Jaffe,¹²⁹ in an analysis of 500 cases of myocardial infarction, found that hypertension occurred in more than one half of the men and four fifths of the women. They concluded that hypertension is a definite etiologic factor in coronary occlusion. This incidence was definitely greater in their group of cases than that noted in the general population. It occurred five to eight times as often among men with hypertension as among patients with normal blood pressure. Both ratios increase with age in the same proportion.

Newburger and Peters¹³⁰ reported 4 cases of capillary glomerulosclerosis and reviewed the clinical records in previously reported cases. Diabetes, hypertension and albuminuria constitute the features of this syndrome, although edema, heart failure, renal failure and anemia are often present. Hypertension was present for varying periods in all the cases. It usually endured for a considerable period, and in all but 1 case was present as one of the initial findings. It often was of rather severe grade.

Goldblatt, Kahn and Hanzal¹³¹ made observations on the constriction of the abdominal aorta just above the site of origin of both main renal arteries. Little or no immediate effect on blood pressure in the vessels above the site of the clamp was noted, but in about twenty-four hours hypertension developed. Below the site of the clamp a fall in pressure occurred in the femoral arteries. Within twenty-four hours the mean pressure in the femoral artery also began to rise, at the same time that the pressure in the carotid artery increased. In some animals the pressure in the femoral artery rose to a level higher than normal,

129 Master, A. M., Dack, S., and Jaffe, H. L. Age, Sex and Hypertension in Myocardial Infarction Due to Coronary Occlusion, *Arch Int Med* **64** 767 (Oct) 1939.

130 Newburger, R. A., and Peters, J. P. Intercapillary Glomerulosclerosis: A Syndrome of Diabetes, Hypertension and Albuminuria, *Arch Int Med* **64** 1252 (Dec) 1939.

131 Goldblatt, H. A., Kahn, J. R., and Hanzal, R. F. Studies on Experimental Hypertension. The Effect of Construction of the Abdominal Aorta Above and Below the Site of Origin of Both Main Renal Arteries, *J Exper Med* **69** 649 (May) 1939.

even though the abdominal aorta was occluded. If the aorta was constricted below the site of origin of the renal artery there was no rise in blood pressure above the level of the clamp. The pressure below usually fell and tended to remain low. The authors concluded that the rise in blood pressure occurring under these conditions is due to renal ischemia, regardless of the presence of renal insufficiency.

The number of clinical reports¹³² of cases in which disease of the renal arteries in man is associated with hypertension, as well as with urologic types of hypertension, seems to be increasing as the relationship between such disorders is more widely recognized. It is becoming apparent that in all cases of early hypertension disease of the renal arteries should be considered and excluded.

Weiss and Parker¹³³ have written an excellent monograph on pyelonephritis and have emphasized the relation of persistent hypertension to the chronic and healed forms of the disease, with which arterial hypertension is frequently associated. It may be associated with adequate or impaired renal function, and it is often of severe grade, with all the characteristic findings and symptoms. It is important to note that hypertension did not occur with renal tuberculosis or hydronephrosis unless pyelonephritis was also present.

Apparently, the pathologic factor necessary for the appearance of hypertension is inflammatory disease of the vessels, and such lesions as acute arteritis, arteriolitis, productive endarteritis and necrotizing arteriolitis, together with hyperplastic arteriosclerosis, were commonly noted in the cases studied. In the cases in which hypertension was present it did not differ from that of essential hypertension without demonstrable clinical disease of the kidneys.

Whether the changes in the arterioles of the kidneys result from primary disease of the kidneys or primary angiospasm of undetermined origin, the result is the same. If the spasm is persistent, organic changes in the arterioles occur and hypertension is persistent. If the endo-

132 Blackman, S. S., Jr. Arteriosclerosis and Partial Obstruction of the Main Renal Arteries in Association with "Essential" Hypertension in Man, *Bull. Johns Hopkins Hosp.* **65** 353 (Nov.) 1939. Mulholland, S. W. Hypertension's Challenge to Urology, *J. Urol.* **42** 957 (Dec.) 1939. Nesbit, R. M., and Ratliff, R. K. Hypertension Associated with Unilateral Nephropathy, *ibid.* **43** 427 (March) 1940. MacKenzie, D. W., and Seng, M. I. Urological Aspects of Hypertension, *Surg., Gynec. & Obst.* **70** 578 (Feb., no. 2A) 1940. Maher, C. C., and Mosika, P. H. Urologic Hypertension, *J. Urol.* **41** 893 (June) 1939. Blackman, S. S., Jr. Arteriosclerosis and Partial Obstruction of the Main Renal Arteries in Association with "Essential" Hypertension in Man, *Bull. Johns Hopkins Hosp.* **65** 353 (Nov.) 1939. Stewart, C. F. Arteriosclerosis of the Renal Artery Orifices with Severe Hypertension, *J. A. M. A.* **114** 2099 (May 25) 1940.

133 Weiss, S., and Parker, F., Jr. Pyelonephritis. Its Relation to Vascular Lesions and to Arterial Hypertension, *Medicine* **18** 221 (Sept.) 1939.

thelium becomes proliferative and necrosis occurs, the disease pursues a malignant course

Page¹³⁴ reported another method for the induction of arterial hypertension experimentally in animals. This is accomplished by the production of severe fibrocollagenous perinephritis, through wrapping the kidney in cellophane. By this method the renal pedicle is left free, and renal ischemia is produced by the constricting perirenal fibrosis, which affects the structure of the kidney directly. Removal of such a kidney, if the other kidney is normal, abolishes the hypertension. Denervation of the renal pedicle does not prevent the development of hypertension. Bilateral removal of the adrenal glands abolishes the increase in pressure, but slight hypertension persists if the animals are treated with adequate amounts of sodium chloride and renal cortical extract. This indicates that perinephritis may be a factor in the production of hypertension in man.

Page¹³⁵ also demonstrated that constriction of the aorta may produce hypertension in dogs if the constriction is above the level of the renal arteries, if below, hypertension does not occur. It was noted that to secure such a rise in blood pressure, the aorta must be constricted just above the renal arteries. This is in agreement with work previously reported. If, however, the aorta is constricted or occluded at the arch of the aorta, near the site of constriction which is present in human coarctation, hypertension does not develop. There is some reduction in pressure distal to the occlusion, with a tendency to return to normal later. After several days the pressure in the femoral artery may fall progressively without reduction of pressure in the carotid artery. The failure to produce persistent hypertension under these conditions is attributed to the fact that in dogs an extensive collateral circulation readily develops. If the constriction is made within a short distance below the origin of the renal vessels and the aorta is occluded or constricted at the level of the diaphragm, hypertension occurs. Removal of the kidneys reduces or abolishes hypertension. Page expressed the opinion that these experiments suggest that the hypertension which occurs in coarctation of the human aorta is actually of renal origin.

Another method¹³⁶ for the production of hypertension by the prevention of renal hypertrophy was described by Greenwood, Nassim and Taylor.

134 Page, I. H. Production of Arterial Hypertension by Cellophane Perinephritis, *J. A. M. A.* **113** 2046 (Dec. 2) 1939.

135 Page, I. H. The Effect of Chronic Constriction of the Aorta on the Arterial Blood Pressure in Dogs. An Attempt to Produce Coarctation of the Aorta, *Am. Heart J.* **19** 218 (Feb.) 1940.

136 Greenwood, W. F., Nassim, R., and Taylor, N. V. The Production of Hypertension by the Prevention of Kidney Hypertrophy, *Canad. M. A. J.* **41** 443 (Nov.) 1939.

Short and Johnson,¹³⁷ in studying the relation of overweight to blood pressure, expressed the opinion that as a factor in hypertension overweight has been regarded as more important than it actually is. This they concluded in spite of their observation that the incidence of hypertension in a large group of overweight persons seemed to be increased, but to a less degree than that reported by others. The increase seemed to be more evident in the diastolic than in the systolic readings.

In contrast to this, Wood and Cash¹³⁸ found in dogs with experimental hypertension that the systolic pressure rose with gain in weight and declined with loss in weight. The diastolic pressure varied but little. They expressed the belief that overweight may be a factor of some importance in elevation of the systolic pressure.

It would seem that comparison of these results with those in man is hardly justifiable.

De Wesselow and Thomson¹³⁹ studied the serum electrolytes, particularly sodium, potassium and calcium, in cases of hypertension. It was found that changes in the diet intake of these substances had little or no effect on the variations in blood pressure in either normal or hypertensive persons. Large quantities of sodium seemed to result in a rise in blood pressure, while very large amounts of potassium caused a fall. These effects seem to be best explained by changes in blood volume and the effect of potassium in large amounts on the heart.

It appears that these salts are important in the regulation of pressure in Addison's disease or other disorders of the adrenal glands. When these structures are intact but little effect is noted in the blood pressure level, even when fairly large amounts of the salts are administered.

A CRITICAL REVIEW OF THE SURGICAL TREATMENT

BY DR. de TAKÁTS AND DR. BECK

This year's library output represents a consolidation and extension of the achievements of previous years, hence reviews of monographs and symposiums dominate the field. The articles selected for review are those which contain material of interest for the nonsurgical reader.

137 Short, J. J., and Johnson, H. J. An Evaluation of the Influence of Overweight on Blood Pressures of Healthy Men. A Study of 3,516 Individuals Applying for Periodic Health Examinations, *Am J M Sc* **198** 220 (Aug) 1939.

138 Wood, E. J., Jr., and Cash, J. R. Obesity and Hypertension. Clinical and Experimental Observations, *Ann Int Med* **13** 81 (July) 1939.

139 de Wesselow, O. L. V. S., and Thomson, W. A. R. Study of the Serum Electrolytes in Hypertension, *Quart J Med* **8** 361 (Oct) 1939.

PARAVERTEBRAL BLOCK

The injection of procaine or alcohol into the region of the ganglionated trunk of the sympathetic nervous system is still gaining in favor. In his thought-provoking monograph on the surgery of pain, which has recently been translated, Leriche¹⁴⁰ summarized many years of clinical research on the diagnostic and therapeutic value of the abolition of pain by injections of procaine into the sympathetic ganglions. These have been carried out in cases of facial neuralgia that is not trigeminal, of post-traumatic spreading neuralgia, of causalgia in painful amputation stumps, of pain due to vasoconstriction, of angina pectoris and of various types of visceral pain. The critical reader may find a few gaps in the author's marshaled evidence, but there can be no doubt about the profound influence he has exerted on the surgery of the autonomic nervous system and on efforts to control pain.

In last year's review we noted the emphasis of Ochsner and DeBakey on the importance of vasospasm as a readily controllable factor in the prognosis and treatment of peripheral vascular disease. In a critical survey¹⁴¹ they drew attention to the relative ease and safety with which injections can be made in paravertebral ganglions, even in outpatient clinics. Their treatment of 22 patients with thrombophlebitis by procaine block is described and illustrated in an article¹⁴² in which conservative and radical methods of prophylaxis are discussed. Equally impressed with the frequency and importance of vasospastic states was Homans,¹ who in his recent classic monograph on circulatory diseases of the extremities devoted considerable space to the discussion of the technic and results of paravertebral injections.

Collens and Wilensky³ and Samuels¹⁴³ took a different view of vasospasm and did not place its release in the center of therapeutic aims. It may well be that the intermittent venous hyperemia induced by the former and the hypertonic solution of sodium chloride employed by the latter obtain the same objective, but by different routes. As Ochsner and DeBakey¹⁴¹ pointed out, "the paravertebral block is actually the more conservative procedure, because the patient may be completely relieved from vasospasm in a few minutes and thus the

140 Leriche, R. *The Surgery of Pain*, translated and edited by A. Young, Baltimore, Williams & Wilkins Company, 1939.

141 Ochsner, A., and DeBakey, M. *Peripheral Vascular Disease. A Critical Survey of Its Conservative and Radical Treatment*, Surg., Gynec. & Obst. **70** 1058 (June) 1940.

142 Ochsner, A., and DeBakey, M. *Therapy of Phlebothrombosis and Thrombophlebitis*, Arch. Surg. **40** 208 (Feb.) 1940.

143 Samuels, S. S. *The Diagnosis and Treatment of Diseases of the Peripheral Arteries*, ed. 2, New York, Oxford University Press, 1940.

patient is saved the loss of time and expense required by the prolonged therapy of vascular exercises."

There really need be no conflict between these methods, in our experience¹⁴⁴ the intermittent venous hyperemia which gradually increases the capacity of the venocapillary bed may be carried out in the home by a simple, inexpensive apparatus, it acts much better in a limb the sympathetic vasoconstrictors of which have been previously blocked. But the paravertebral block is safe and effective only in the hands of those who can visualize the structures to be passed by the needle, surgical experience with exposure of the ganglionated trunk is of great help in the performance of this chemical block. As Homans¹ stated "The operator must have the ability to visualize the spinal column, its transverse processes and the ribs and to know where the point of his needle is going. Above all he must have the disposition suited to local anesthesia, the gentleness, deliberation and power of assurance without which injections of procaine are a trial to the patient, in some cases, an agony."

A valuable suggestion by Gage¹⁴⁵ is the use of sympathetic block before the surgical attack on an aneurysm. For the lower extremity a paravertebral block with alcohol was advised, while for the upper extremity preoperative and postoperative infiltrations of procaine into the stellate ganglion were suggested. Among 15 patients so treated not a single case of gangrene developed. Sympathetic block aids the development of an efficient collateral circulation, increases the total blood flow to the extremity and prevents postoperative spasm. The aneurysmal sac may decrease, and intrasaccular clotting can occur.

SURGICAL TREATMENT OF VENOUS THROMBOSIS

During the last few years certain principles have crystallized the wider adoption of which might shorten convalescence, diminish permanent edema and lessen the danger of pulmonary embolism. The occurrence of vasospasm, resulting in pain and edema, has already been mentioned and its release by paravertebral block described¹⁴². The ligation of the femoral vein proximal to a septic thrombus, followed by a prompt drop in the pulse rate and the temperature to normal, has been discussed in previous reviews and another instance cited by Oschsner and DeBakey¹⁴². Taylor¹⁴⁶ tied the external iliac vein in a

144 de Takats, G., Beck, W. C., and Roth, E. A. The Neurocirculatory Clinic. I. Peripheral Vascular Disease, *Ann Int Med* **13** 957 (Dec.) 1939.

145 Gage, M. The Development of Collateral Circulation in Peripheral Aneurysms by Sympathetic Block, editorial, *Surgery* **7** 792 (May) 1940.

146 Taylor, K. P. A. Pulmonary Emboli Following Injection of Varicose Vein. Control by Ligation of External Iliac Vein, *Am J Surg* **45** 145 (July) 1939.

patient who had a pulmonary infarct following the injection of varicose veins. The extraction of a bland, nonseptic thrombus from the femoral vein through an opening in the saphenous vein has been reported.¹⁴⁷ Homans¹ called attention to a treacherous, often unrecognized, site of thrombosis in the deep veins of the lower part of the leg involving the posterior tibial, anterior tibial or peroneal system. Because there are many of these veins, little or no sign of venous stasis occurs. If elevation for ten days does not result in complete disappearance of soreness, swelling or cyanosis, Homans advocated the division of the femoral vein below the renal profundae. In his experience, cyanosis or edema after the procedure is slight, if present at all.

This type of thrombosis, as Homans emphasized, is so dangerous that the division of the femoral vein should not be unduly delayed. Of 4 such patients seen recently by one of us (G. de T.), 3 had massive pulmonary infarcts and 2 died. The typical phlegmasia alba dolens, "the iliofemoral thrombophlebitis," however, carries only a slight incidence of pulmonary embolism,¹⁴⁷ and it is much more difficult to decide on surgical intervention in such cases. More than two massive pulmonary infarcts, however, call for a proximal division of the vein, this must be made at the level of the common iliac vein to exclude the hypogastric bed from releasing emboli. Possibly the wider application of heparin will increasingly restrict the indication for proximal venous ligation.

HEPARIN IN THE SURGICAL TREATMENT OF BLOOD VESSELS

Murray^{102a} has recently given the latest experiences of the Toronto group with the intravenous injection of purified heparin in treatment of vascular diseases. To date his group has given preventive treatment to 440 patients in the hospital, in none of whom thrombosis and embolism occurred. Patients with thrombophlebitis were thought to be definitely improved by the treatment, within a few hours after administration pain diminished and the temperature had begun to fall. Murray gained the impression that there has been less persistent edema in the treated than in the control group. While pulmonary embolism occurred in 15 per cent of 300 control subjects, it did not occur in 91 patients to whom heparin was given. Patients with migrating phlebitis, however, did not respond so well.

Twenty-nine patients with pulmonary embolism were treated, none of these died. The dyspnea and other signs improved rapidly, and within twenty-four hours the patients seemed definitely on the road to

¹⁴⁷ de Takáts, G., and Jesser, J. H. Pulmonary Embolism. Suggestions for Its Diagnosis, Prevention and Management, *J. A. M. A.* **114** 1415 (April 13) 1940.

recovery Some of the patients were of the type for which prognosis seemed extremely bad

Peripheral arterial embolectomy was successful in 12 cases in which heparin was used Heparin was injected into the vessel at the site of operation, and the injection was continued intravenously for from three to fourteen days In 1 case a venous graft was placed in an artery, which remained patent In 6 cases of mesenteric thrombosis in which extensive resections of the bowel were required heparin was given Four of the patients lived, 1 died of bronchopneumonia and 1 of peritonitis Eight splenectomized patients were given heparin, as it is known that portal thrombosis is a definite factor in mortality In none did thrombosis develop

McClure and Lam¹⁴⁸ reported their experience in use of heparin in 11 cases Eight of the patients had pulmonary embolism, and all recovered One patient with popliteal embolism and 1 with arterial thrombosis received heparin The authors pointed out that considerable variation in the amount of heparin is necessary to prolong the clotting time to an optimum level

As stated in our last review, the clinical use of purified heparin is one of the far reaching contributions to vascular surgery The price still prohibits its general application for prolonged periods Until a cheaper product or a new synthetic drug becomes available, one may have to resort to shorter periods of application or to substitution with leeches The treatment of thrombophlebitis with leeches was revived by Termier (cited by Page¹³⁵) in 1922 Mahorner and Ochsner¹⁴⁹ summarized the extensive bibliography up to 1933 and reported several cases of their own Ochsner still employs the method in treatment of portal thrombophlebitis¹⁴² As some reports have indicated, however, that embolism may be favored during its application, the procedure must be used with caution In our own experience, leeches slightly prolong systemic coagulation time and seem to hasten the disappearance of edema Purified hirudin might be more advantageous than the cumbersome use of leeches, which may produce infection Another substitute for heparin may be some inorganic solutions of sulfur, such as sodium thiosulfate or sodium tetrathionate, which in the experience of Theis and Freeland³⁰ are useful in relief of thrombotic and vasospastic states and which have been found to increase the glutathione content of the liver and blood Glutathione is a catalyst of oxidation which activates inactive oxyhemoglobin Its relation to the clotting phenomenon is yet

148 McClure, R. D., and Lam, C. R. Experiences in Heparin Administration, *J. A. M. A.* **114** 2085 (May 25) 1940

149 Mahorner, H. R., and Ochsner, A. The Use of Leeches in the Treatment of Phlebitis and the Prevention of Postoperative Embolism, *Ann. Surg.* **98** 408 (Sept.) 1933

unclear, clinically, however, rapid regression of attacks of thrombophlebitis, especially of the migrating type, has been observed by one of us (G de T) It has been suggested that the injection of the sulfur compounds actually mobilizes the patient's own heparin¹⁵⁰

ANEURYSMS AND ANGIOMAS

A number of interesting case reports¹⁵¹ reveal the difficulties of management, especially in cases of the congenital variety The cavernous hemangioma in Matas' case recurred eleven years after disarticulation of the shoulder The only new principle introduced in this technically difficult field is the employment of sympathetic paralysis, temporary or permanent, before the radical attack on the aneurysm is undertaken, this procedure facilitates the development of collateral circulation to such an extent that ligations and excisions can be undertaken with more safety It also seems to facilitate spontaneous thrombosis in the aneurysmal sacs by decreasing peripheral resistance¹⁵²

CERVICAL RIB AND THE SCALENUS SYNDROME

Two papers containing a total of 41 new cases of this syndrome have recently been presented at a meeting of the Southern Surgical Association by Donald and Morton¹⁵³ and by Aylesworth¹⁵⁴ The recognition of symptoms due to the compression of the brachial plexus and the subclavian artery by the scalenus anterior muscle has increased in frequency in the last few years, even though Murphy as early as 1906 drew attention to the possible role of the scalenus anterior muscle in the production of symptoms arising from cervical ribs In 16 of the 21 cases reported by Donald and Morton, the disturbance was not associated with a cervical rib Trauma, occupational strain and improper posture precipitated the symptoms The results following the section of the scalenus muscle were excellent In 14 of the cases there was complete relief, in only 2 did symptoms recur Many mild conditions respond to conservative therapy and need no operation Aylesworth emphasized trauma as an etiologic factor in 80 per cent of 20 cases In 12 cases

150 Bancroft, F R, in discussion on Murray, G D W, and Best, C H The Use of Heparin in Thrombosis, *Ann Surg* **108** 173 (Aug) 1938

151 Matas, R Congenital Arteriovenous Angioma of the Arm Metastasis Eleven Years After Amputation, *Ann Surg* **111** 1021 (June) 1940 Gatch, W D Case of Large False Aneurysm of the Right Subclavian Artery Successfully Treated by a Modification of the Matas Operation, *ibid* **111** 1046 (June) 1940

152 Discussion on papers of Matas and Gatch, *Ann Surg* **111** 1052 (June) 1940 Discussion on Gage¹⁴⁵

153 Donald, J M, and Morton, B F The Scalenus Anticus Syndrome With and Without Cervical Rib, *Ann Surg* **111** 709 (May) 1940

154 Aylesworth, K H The Cervicobrachial Syndrome A Discussion of the Etiology with Report of Twenty Cases, *Ann Surg* **111** 724 (May) 1940

operation was performed with satisfactory results, except in 1 case in which the condition was unsuitable for tenotomy. In order to simplify the nomenclature and to express a more correct symptomatology, he suggested the term "cervicobrachial syndrome."

In a thoughtful discussion, Patterson¹⁵⁵ enumerated many pitfalls which may beset those who regard any pain in the arm or shoulder as due to compression by the scalenus muscle. It has been our custom to make a diagnosis by exclusion. Subdeltoid bursitis, arthritis of the shoulder, cervicodorsal arthritis of the spine, tuberculous lymph glands of the neck, apical tuberculosis with adhesive pleurisy at the first rib and other conditions have been observed to simulate this syndrome. It may, of course, be argued that all these conditions are capable of producing reflex spasm in the scalenus anterior muscle. If this is present the diagnostic test of Gage,¹⁵⁶ in which the scalenus muscle is infiltrated with procaine, will reveal it. Nevertheless, by elimination of the source the muscle spasm often relaxes. While the success is dramatic, when carried out in the properly selected case, it is to be expected that in a number of cases tenotomy is unnecessary and will yield no results. It is important to prevent regeneration by excision of a segment of muscle and to treat the chronic brachial neuritis with rest and thiamine chloride after the operation.

SYMPATHECTOMY IN TREATMENT OF PERIPHERAL VASCULAR DISEASE

Smithwick,¹⁵⁷ in a continuation of his studies, stated that the arguments for and against sympathetic ganglionectomy in the treatment of peripheral vascular disease emphasize the importance of complete denervation by a preganglionic procedure. In his operation he divides the sympathetic trunk below the third dorsal ganglion and resects the second and third intercostal nerves, following them to their anterior and posterior roots. The posterior roots are divided just proximal to its ganglion. This results in satisfactory denervation of the upper extremity. For sympathetic denervation of the lower extremity the second and third lumbar ganglia and their rami are excised. Interesting and characteristic changes take place after preganglionic sympathectomy. For the first few days after operation the extremity is dry, warm and of excellent color. Reflex sweat and vasomotor activities are abolished. Between the third and the fifth day a sudden burst of sympathetic activity

155 Patterson, R. H. Cervical Ribs and the Scalenus Muscle Syndrome, *Ann Surg* **111** 531 (April) 1940.

156 Gage, M. Scalenus Anticus Syndrome. A Diagnostic and Confirmatory Test, *Surgery* **5** 599 (April) 1939.

157 Smithwick, R. M. Surgical Intervention on the Sympathetic Nervous System for Peripheral Vascular Disease, *Arch Surg* **40** 286 (Feb.) 1940.

takes place. The extremity begins to perspire, becomes cooler and is often discolored. This is interpreted as a spontaneous outflow of impulses from the decentralized sympathetic ganglions. Actually, we have never seen the phenomena when the ganglions were also removed, except immediately after the operation. During the second and third weeks the surface temperature gradually falls until it reaches a stable level. Sensitivity to epinephrine appears and is probably largely due to the fall in surface temperature. Months or years after operation a well sympathectomized extremity should have a high surface temperature with little or no rise on blocking with procaine hydrochloride. There is complete abolition of reflex vasomotor and sweating responses.

When the operation is incomplete the surface temperature is only slightly elevated, or not at all. Peripheral nerve block results in a marked rise in cutaneous temperature. Reflex sweating and vasomotor responses are present. Sensitivity to epinephrine will not appear.

From six months to a year and a half after what is thought to be a complete operation a "relapse" may take place. The situation is undoubtedly due to partial regeneration of sympathetic fibers. Smithwick found that the vasomotor reflex was absent in all of the 8 cases in which relapse occurred, but that reflex sweating was present. While vasomotor responses were determined with the help of a photoelectric cell, the sweat responses were studied by measuring cutaneous resistance and the psychogalvanic reflex. The significance of the findings is not clear.

The clinical results depend, in addition to the completeness of pre-ganglionic denervation, on the degree of local fault in the vessels. Results have been excellent in the early stages. When there are sclerodermatous changes, calcification of tissues or destruction of bone, the results are inferior. These observations confirm those of Patterson Ross, which have been reviewed in former years.

In thromboangitis obliterans the addition of sympathectomy to the nerve crushing and minor amputations previously employed has markedly decreased the percentage of major amputations, this is especially true when the popliteal artery is patent. While, obviously, the most brilliant results are obtained in cases of purely vasospastic disorders, worthwhile improvement may often follow in cases in which both organic obstruction and spasm of arteries are known to exist.

The degree of structural involvement, the technic of operation and the preoperative diagnosis were the three factors in an analysis of the percentage of failures.¹⁵⁸ A method of extended cervical sympathectomy has been described in which the intermediate ganglion, the vertebral

158 de Takáts, G. Analysis of Results Following Sympathectomy for Peripheral Vascular Disease, *Am J Surg* 47:78 (Jan) 1940.

plexus and the ganglionated dorsal chain from the stellate to below the third thoracic ganglion have been excised in 21 cases to date, with results that in our hands are equal, if not superior, to the preganglionic sections. The importance of the first white ramus in supplying vasomotor fibers to the upper extremity has not yet been definitely established. A satisfactory number of cases in which the preganglionic type of operation is done on one side and the extended cervicodorsal sympathectomy on the other should settle this technical question.

The post-traumatic dystrophy of extremities, which is such a stumbling block to medicolegal experts, has been studied by Haldbo,¹⁵⁹ who expressed the belief that the severe forms resisting conservative therapy should be treated by sympathetic denervation.

Ochsner and DeBakey¹⁴¹ gave a complete review of the various approaches to the cervicodorsal and lumbar sympathetic trunks, together with the history of their development. The new and little known approach of Leriche, Percira and DeBakey¹⁶⁰ was again described. In addition to excluding neurogenic impulses to the lower extremity, they employ section of the splanchnic nerve to decrease the reflex secretion of epinephrine, which may play a role in vasospastic states of the extremities. Our experience with this approach, to which occasionally resection of the tip of the twelfth rib may be added, has been favorable.

EMBOLECTOMY

The valuable addition of heparin in the postoperative care of patients who have had arterial sutures has already been discussed.^{102a} Haimovici¹⁶¹ assembled in a small practical monograph the clinical applications of recent research on acute arterial occlusions. He pointed out that the embolus sets up a reaction of the vessel wall within the first ten to twelve hours, which again stimulates extension of the thrombosis. The intimal lesion, thus produced, is responsible for secondary thrombosis after the extraction of the clot; the adventitial reaction is the starting point of vasoconstrictor reflexes which affect the main vessel and its collaterals. The extension of thrombosis blocks a number of collaterals, the patency of which might save the limb from gangrene. Embolectomy is therefore urged within the first ten to twelve hours following the vascular accident if known conservative measures fail. If this period

159 Haldbo, H. Post-Traumatic Dystrophy of Extremities, *Nord med* 3: 2053 (July 8) 1939.

160 Leriche, R., Percira, S., and DeBakey, M. La résection des nerfs splanchniques. Technique et résultats de quelques observations de thromboangite oblitérante, hypertension paroxystique, megacolon et dolichocolon, *Med Contemp*, July 1937, no. 27.

161 Haimovici, H. Les occlusions artérielles des membres, Paris, Masson & Cie, 1939.

has been missed, arteriectomy (see our previous reviews) is advocated, if this should fail to improve the circulation, lumbar sympathectomy by procaine block or surgical excision is in order

It may seem like overzealous activity to perform multiple operations on a patient whose cardiovascular system is crippled by a myocardial thrombus, a mitral stenosis with vegetations or ulcerating endocarditis. Nevertheless, this seems justifiable if a patient's leg can be saved from amputation. The indifference of physicians to a situation of the utmost urgency in cases of acute arterial occlusion can be overcome only by the demonstration of the dramatic results which may be obtained by an early and skilful attack on the occluded artery. It is true that roughly 50 per cent of arterial emboli do not lead to gangrene, but these can be readily recognized in the first few hours by their favorable response to physical and drug therapy.

SURGICAL TREATMENT OF HYPERTENSION

Progress in the surgical therapy of hypertension is continuing from several sources. Better understanding and clearer classification of this syndrome have been brought about by the studies of Schroeder and Steele,¹⁰⁸ who classified 218 cases as those of renal, neurogenic, endocrine, vascular and unclassified origin. The surgeon will greatly benefit from a better understanding of the nature of the hypertension with which he is dealing. The point should be made that not in all cases is the hypertension due to the presence of Goldblatt kidneys.

A report of the effect of supradiaphragmatic section of the splanchnic nerves has been made by Braden and Kahn.¹⁶² In a review of 264 cases of Peet's series in which the patients were followed from six months to five years, they found an operative mortality of 3 per cent and a postoperative mortality rate of 23 per cent. In 43 per cent of the patients with recurrence the blood pressure was significantly reduced, 84 per cent were able to return to their former activities, and 87 per cent had symptomatic relief. In their experience selection of cases is not possible with the present methods.

Adson,¹⁶³ on the other hand, discussed his experience with sub-diaphragmatic splanchnic resection. He used the depressor effect of sedatives and the cold pressor test as valuable guides in selecting patients for operation. Of an unselected group of 156 patients, 1 died, 20 per cent recovered normal blood pressure and 35 per cent obtained marked reduction in pressure. No effect on blood pressure was obtained in 20

¹⁶² Braden, S, and Kahn, E. A. Surgical Treatment of Hypertension. Preliminary Report of Study and Results in Two Hundred and Sixty-Four Cases, *Yale J Biol & Med* **11** 449 (May) 1939.

¹⁶³ Adson, A. W. Classification of Hypertension. Prognosis and Management, *Mil Surgeon* **84** 537 (June) 1939.

per cent, and temporary lowering was found in 25 per cent. Symptomatic relief was obtained in 85 to 95 per cent of the two groups showing favorable responses.

It is remarkable that two surgeons using different technical approaches and different selections of cases should have such similar results. Roughly 50 per cent of the patients had objective evidence of improvement, whereas 85 per cent reported marked symptomatic relief.

Davis and Barker¹⁶⁴ found that approximately 50 per cent of their hypertensive patients showed both objective and symptomatic relief after sulfocyanate therapy. After a good initial response, 25 per cent of the patients became refractory, and much larger doses were required to maintain a satisfactory cyanate level. In the remaining group a gradual rise in blood pressure occurred, in spite of a constantly maintained and seemingly adequate concentration of cyanate in the blood. The authors considered only surgical treatment for patients who were resistant to cyanates and reported 6 cases of this type. In these cases bilateral supradiaphragmatic splanchnic section alone failed to decrease the blood pressure or to alter the chemical constituents of the blood. In such cases, however, they could obtain a satisfactory response to cyanates, which was not possible before the operation. They did not attempt to explain this acquired sensitivity, although possible reasons were suggested.

Smithwick,¹⁶⁵ in his recent report based on experience with approximately 150 patients suffering from hypertension, established the following criteria for successful sympathectomy. The operation must be complete, it should be preganglionic in type and extensive enough to guard against future regeneration. He described an operation which removes the entire splanchnic nerve from its roots to its entrance into the celiac ganglion, divides all its branches to the aorta and excises the ganglionated trunk with the communicating ramus of the ninth dorsal to the second lumbar nerve, inclusive. This seems to be the minimal procedure which consistently produces the characteristic postural hypotension that the author establishes as a criterion of successful splanchnic denervation. With this standardized technical procedure he has now attacked different stages of the disease, which division is largely based on changes in the eyegrounds. The less advanced stages have shown far better response than the more advanced ones.

The operation of Smithwick is preganglionic in type, it is so extensive that individual variations, for which the sympathetic nervous system

164 Davis, L., and Barker, M. H. Clinical and Experimental Experiences in the Surgical Treatment of Hypertension, *Ann Surg* **110** 1016 (Dec.) 1939.

165 Smithwick, R. H. A Technique for Splanchnic Resection for Hypertension, *Surgery* **7** 1 (Jan.) 1940.

is notorious, will not result in escape from section, moreover, regeneration over such a wide area is not to be expected. For the first time, we believe, a method of total splanchnic nerve section has been presented, this may explain many of the failures in previous series. The factor of the stage of the disease has also been taken in account, with the help of which it may reasonably be possible to predict the results of operation in the individual case. Smithwick's work will undoubtedly give new impetus along this line of clinical research.

Ascroft¹⁶⁶ recommended splanchnic resection only when the hypertension is labile and of short duration, even then, he stated that the results are unpredictable. He suggested nephro-omentopexy, in addition to sympathectomy, as a means of increasing renal arterial supply.

Because of the beneficial effects of collateral circulation on the experimental hypertension produced by renal ischemia, nephro-omentopexy was suggested in treatment of human subjects and was carried out, in the first case four years ago¹⁶⁷. The patient is still alive, and since that time 4 others have been subjected to decapsulation and scarification of the kidney, which was then wrapped up in omentum or muscle flaps. Bruger and Carter,¹⁶⁸ in a preliminary note, reported 8 cases in which nephro-omentopexy was undertaken on the right kidney in man. In 1 case, in which autopsy was later performed, they were able to demonstrate particles of india ink in the omentum when the kidney was perfused through the renal artery. However, from their histologic sections only venous drainage of the kidney into the omentum could be demonstrated. Only prolonged observations will decide the merits of this procedure. It seems that simple decapsulation will not bring about any increase in circulation¹⁶⁹ and that incisions into the cortex followed by omental or muscular implants must be made to facilitate vascular connections.

AMPUTATIONS

Williams and O'Kane¹⁷⁰ presented a simple classification of gangrene of the extremities in patients with diabetes. They are vascular, inflammatory and mixed. The degree in which the vascular and the inflammatory component is present will decide the therapy employed.

166 Ascroft, P. B. The Surgical Treatment of Arterial Hypertension, *Lancet* **2** 113 (July 15) 1939.

167 de Takats, G. Revascularization of the Nephrosclerotic Kidney, *Proc Central Soc Clin Research*, 1939, p. 49.

168 Bruger, M., and Carter, R. F. Evidence of Communication Between Renal and Omental Blood Vessels Following Nephro-Omentopexy for Arterial Hypertension in Men. Preliminary Note, *Am J M Sc* **197** 832 (June) 1939.

169 Goldberg, S., Rodbard, S., and Katz, L. N. Increased Collateral Blood Supply to the Kidney in Renal Hypertension, *Surgery* **7** 869 (June) 1940.

170 Williams, F. W., and O'Kane, T. J. Clinical Classification of Lesions of Lower Extremities Associated with Diabetes, *Arch Surg* **40** 685 (April) 1940.

Faxon¹⁷¹ reported on 204 unilateral and 58 bilateral amputations done in 530 cases of obliterative vascular disease. In 52 instances the patients were seriously ill and a guillotine amputation was done, three weeks later reamputation was performed in 84 per cent of the surviving patients. A primary closed amputation was done in 40 per cent of the cases. In amputations for Buerger's disease amputation below the knee was usually unsuccessful, even in the presence of a pulsating popliteal artery, in 75 per cent reamputation was necessary. The Gritti-Stokes amputation is preferred, and this can be done even in the absence of a popliteal pulse. The circular, inverted, funnel-shaped amputation just above the patella, however, gave the least postoperative reaction and is thus the safest for feeble patients.

In a report of the largest series of amputations for diabetic gangrene ever reported, McKittrick¹⁷² described the organization at the New England Deaconess Hospital for the care of patients with diabetes mellitus and gangrene and discussed 972 cases of diabetic vascular deficiency. The mortality in the hospital was 94 per cent. The mortality after major amputations was 13.9 per cent. Bilateral amputations were done in 16 per cent of the cases. The mortality after the second amputation was definitely lower than that after the first. The causes of death in 73 cases were: infection, 40 per cent, cardiorenal diseases, 40 per cent, and pulmonary complications, 18 per cent, in half of which the condition was due to embolism. Patients who accepted bilateral amputation may look forward to nearly twice the life expectancy of those who had only one leg amputated. Of 33 patients who refused amputation, 11 patients survived later amputation, 20 died either of progressive gangrene or after amputation elsewhere, 1 had slow healing, but could never walk on his foot, and 1 died of coronary thrombosis four years after an amputation.

Taylor¹⁷³ reported on 113 amputations, with a case mortality of 37.6 per cent. Forty-six of the deaths were due to infected stumps, in 63 per cent of the survivors stump necrosis and suppuration were noted. This situation was markedly improved by omitting the suture of fascia entirely and suturing the skin only loosely.

Reynolds and one of us (G. de T.)¹⁷⁴ described the determination of the level of amputation with the help of cutaneous temperatures and

171 Faxon, H. A. Major Amputations for Peripheral Arterial Obliterative Disease, *J. A. M. A.* **113** 1199 (Sept. 23) 1939.

172 McKittrick, L. S. Diabetic Gangrene. Review of Nine Hundred and Seventy-Two Cases, *Arch. Surg.* **40** 352 (Feb.) 1940.

173 Taylor, F. W. Arteriosclerotic Gangrene, *J. A. M. A.* **113** 1196 (Sept. 23) 1939.

174 de Takats, G., and Reynolds, J. T. Amputation for Peripheral Vascular Disease, *Arch. Surg.* **40** 253 (Feb.) 1940.

histamine flares. The mortality of 33 per cent was decreased to 7.6 per cent by the prophylactic use of antianaerobic serum and by the adoption of the Callander amputation through the knee joint, 16 of the 20 patients who had Callander amputations were able to wear an artificial limb. The amount of expense and suffering caused by unnecessary delay of unavoidable amputations was discussed. When amputation was done before infection supervened the mortality was markedly lowered.

Although little difficulty was experienced with painful amputation stumps by some of the authors, notably by McKitterick,¹⁷² a number of articles have been devoted to the management of this syndrome. We believe that the best treatment is prophylactic. The large nerves should be crushed and ligated or cauterized and no injections of alcohol should be made into them, nor should they be traumatized in any way.¹⁷⁴ In a series of 250 amputations, Colonna and vom Saal¹⁷⁵ had to do 12 reamputations, they asserted that injection of alcohol into the nerve effectively prevents the formation of neuroma. Virall¹⁷⁶ also paid much attention to the painless stump and the weight-bearing ability. He advised against cutting the nerves short and injecting alcohol into them. Shosberg¹⁰¹ reported on 74 patients with painful amputation stumps who were treated with daily injections of 0.01 Gm of vitamin B₁. Eleven were completely relieved, 39 markedly improved, 10 moderately improved and 7 only slightly benefited. The patients who were helped showed a favorable response after a few injections.

Gallinek¹⁷⁷ discussed the phantom limb. Stimuli applied to the stump are localized partly in the stump and partly in the nonexistent part. Pressing or stroking the stump may relieve this syndrome. The phantom limb seems smaller, although the patient has no definite idea of its aspect or color. The essential factor in producing this sensation is peripheral sensory stimulation, the phantom disappears simultaneously with the relief of pain. A cerebral factor, however, is important, and in the psychotic patient other symptoms are added which produce a type of hallucination.

In analyzing a series of amputations from the Charity Hospital in New Orleans, Veal¹⁷⁸ found that death in 24 of 67 cases was due to pulmonary complications. He expressed the opinion that in most of the cases of pneumonic origin the involvement was embolic. Postmortem

175 Colonna, P. C., and vom Saal, F. Amputation Stumps of the Lower Extremities, *J. A. M. A.* **113** 997 (Sept 9) 1939.

176 Virall, P. J. Amputation Stumps and Artificial Limbs, *Brit. M. J.* **1** 62 (Jan 13) 1940.

177 Gallinek, A. The Phantom Limb, *Am. J. Psychiat.* **96** 413, 1939.

178 Veal, J. R. High Ligation of the Femoral Vein in Amputations of the Lower Extremity, *J. A. M. A.* **114** 1616 (April 27) 1940.

dissections revealed a clot in the stump of the femoral vein in all instances. Certain anatomic variations help the formation of a stagnation thrombus in a long venous stump. Therefore, in 29 consecutive cases he ligated the femoral vein below the saphenofemoral junction. None of the patients so treated had pulmonary complications.

This seems an important suggestion, as pulmonary emboli have caused a small but definite percentage of deaths in all the series reported. In many of the cases of infection, however, the venous periphlebitis may cause a matting together of the femoral artery and vein, the ligation of the latter becomes a delicate procedure.

In general, the lowering of mortality and the elimination of difficult weight bearing, with a better rehabilitation of the patient, are unmistakable trends in this field.

Book Reviews

Syphilis and Its Accomplices in Mischief Society, the State and the Physician By George M Katsainos, M D Paper cover 676 pages devoted to the above title, and 162 pages under the title of "Marriage and Syphilis—A Treatis on Eugenics" Total price \$5 00 Athens, Greece Privately printed ("Kyklos" Publishing Company)

As the title might suggest, this is a rather unusual book Its style is distinctly original and the volume is unique for its forceful bias and its decidedly prejudiced statements It might be considered a philosophic essay rather than a technical treatise on a medicoethical subject The author has gone to great lengths of erudition to distribute on a rather poorly organized framework citations from the Bible, early Greek mythology and the classics, as well as from the works of some of the better known syphilographers of the last decades His book, therefore, becomes somewhat historical in character, but, unfortunately, it contains no bibliography The following quotations may give a clearer insight into the style and character of the book

"Leprosy and syphilis are mirrors, in which man, beholding his reflection is covered with confusion and hides his face in terror, at the sight of his crimes Leprosy and syphilis are the two terrible reagents, which, applied to man, prove him to be a sham, a counterfeit—false and untrue to himself Leprosy and syphilis have shown men to be egotistical, selfish, narrow-minded and cowardly Both these diseases have been, are at present, and will continue to be bugbears and phantasms, which ungrounded fear prevents man from grasping and strangling, or even feeling and becoming acquainted with their texture, much less of seeking out and finding the proper and appropriate means of prevention, since he is powerless to cure"

* * * * *

"But as the drugs by which syphilis is cured are potent chemical poisons, deadly in their effect and requiring the greatest care in their preparation, and even greater care in their application, the quacks have been ruled out of court and scientifically trained and certified physicians have undertaken to carry on their orgies In view of such crimes as are committed on many syphilitic patients today one stands aghast at the number and the magnitude of their victims, and asks himself, "can such things be done by men of science?" Should one attempt to penetrate to the inner sanctuaries and mysteries of extortion and deceit committed today by physicians, he would be persuaded that in comparison with these, Polyphemus and the Lestrigonians, Pityocampes and Procrustes—those bandits of old, would be exonerated and canonized as saints Medicine needs to be purified, the house has fallen into decay and ruins, mouldy, worm-eaten, and infested with vermin, it needs being isolated with all that it contains and, like the house of Socrates in the "Clouds" of Aristophanes, be committed to the flames Society and the state, the one limping the other blind, need a crutch The laws which have hitherto governed us, remnants of the code of Moses, of Solon, of Lycurgus, of Numa, of Tribonianus, of Bacon, no less than of superstition, prejudice, fanaticism, and the unquestioned decrees of the great, need to be renovated It is not enough that we would call to mind the sayings of the Nazarene "Put not new wine into old Bottles," we must put it into practice as well"

The author takes up the symptomatology and treatment of syphilis in a very superficial but decidedly prolix fashion It is somewhat startling to have him discuss the use of arsphenamine (606) and of mercury (without mention of more recent and more popular drugs) as though they constituted all the modern armamentarium of antisymphilitic therapy It might be of academic interest for the reader to reconsider, with the author, points of discussion on the treatment of

syphilis which were thought to have been settled years ago In his "Conclusion" Katsanos states

"A disease, the very name of which is prudishly avoided by the lay press, and the victims of which society hates and condemns, the state prosecutes and punishes, and the medical profession deceives and plunders, and which is impossible to fight in the open, cannot be defeated, conquered, and consequently exterminated"

Although this book was evidently written for lay readers and is interesting because of its original presentation, it cannot be recommended to them because of its many generally unaccepted viewpoints The physician will be disappointed in the book as a scientific work because of its inadequate consideration of the problem, particularly in the light of advances made during the last ten or fifteen years (a period which marks most of the progress in the treatment of syphilis from the social and medical point of view)

The section on "Marriage and Syphilis," which was written in 1922, is better organized It covers much the same material as the first part, but there is more emphasis on heredosyphilis

Provoked Alimentary Hyperglycemia The Mechanism of the Tolerance Test By Joseph Marshall Flint (from the Medical Clinic of the University of Lausanne, Prof Dr L Michaud, Director) **The Effect of the Macallum-Laughton Duodenal Extract upon Hypophyseal Diabetes** By Joseph Marshall Flint and Louis Michaud Pp 77 London, Ontario, Canada A B Macallum, 1939

This work, as indicated by the title, represents the report of two investigations by Dr Flint, who formerly was a professor of surgery at Yale University The author's summaries contain the following material

"Recapitulation—From studies on the intermediate carbohydrate metabolism by the angiotomy method, observations were selected that correspond to the ordinary tolerance test These throw much light upon provoked alimentary hyperglycemia A criss-cross or shift of function between the liver and intestine takes place at the beginning and end of the tolerance reaction by which they exchange roles as yielding and retaining organs vis-a-vis the blood sugar This shift occurs in the following sequence upon the appearance of carbohydrates in the duodenum, absorption of sugar begins and its concentration in the intestine mounts until it passes the retention point and is then yielded to the portal radicals The increase in sugar concentration in the portal blood is the stimulus that induces a change of function in the liver This reduces its yield to the zero point and then begins to retain sugar In consequence, the liver remains during the entire period of the tolerance reaction a potent utilization and hypoglycemic factor as the sugar concentration mounts from the fasting level to the apex of the croquet and back to the initial level again Retention by the organs and tissues during fasting and alimentary hyperglycemia forms the basis of utilization, the removal of sugar from the blood for the various purposes of the intermediate carbohydrate metabolism Following the absorption of sugar from the intestine, a series of organic formulae occur that characterize the various phases of alimentary hyperglycemia In the fasting state, the liver yield equals the combined organic and tissue retention, in the hyperglycemic phase of the tolerance test, the intestinal yield is greater than retention thus increasing the sugar concentration of the blood until at the apex of the reaction (circa 60 minutes)—its maximum concentration—a momentary balance is established when the yield is exactly equalled by retention From this point, the formula changes—organic and tissue retention exceeds the yield—and so the hypoglycemic phase of alimentary hyperglycemia is inaugurated This leads to a gradually diminishing sugar concentration until, as the initial level is approached, the intestine-liver criss-cross recurs in a reverse sense and the original fasting formula is restored It is evident that alimentary hyperglycemia is a resorption phenomenon between the intestine and the organs controlled and equalized by the glycoregulatory mechanism Unusual tolerance reactions such as those obtained from different regimes, fasting, constitutional factors, etc, are to be explained on the basis of changes induced by the endocrine sugar control Similarly, diabetic

tolerance tests are exaggerations of these same factors due to derangements in regulation that vary in degree with the type and severity of the disease. A study of the control will elucidate the possibilities and their effect on the tolerance reaction. In a large sense, defects in the sugar control also indicate the type of diabetes. Overproduction of the anterior pituitary incretions cause hypophyseal diabetes, underproduction of the pancreatic elements lead to pancreatic diabetes, and overproduction of the pancreatic incretions is followed by hyperinsulinism. These are now obvious and self evident consequences of disturbances of the glyco-regulatory system.

"Normally, the function of the Macallum-Laughton extract, derived from the duodenum and pancreas, is (a) to stabilize and maintain the blood sugar level, (b) to synergise the action of insulin, (c) to overcome insulin resistance, (d) to improve the utilization by removing sugar from the blood for the purpose of oxidation, storage, conversion or elimination. The stabilizing effect of the extract on insulin is both short and long term. It tends to prevent the rebound after the transitory action of insulin (6-8 hours) is over. The long term stabilizing or anchor effect may last for months—probably throughout the entire extract cycle. When the action of the extract is induced, a self limited and self determined long term symmetrical physiological action is inaugurated. The pattern once started tends to complete itself providing the factors affecting the blood sugar levels remain at all constant.

"In a word, the Macallum-Laughton extract is normally a stabilizing synergizing factor to insulin, an antinsulin resistant, an antagonist to the anterior pituitary tending to anchor the blood sugar to normal levels and maintain its stability. In diabetes, it may be administered *per ore* alone or in combination with insulin and, by its action, it overcomes the insulin resistance and impaired utilization of hypophyseal diabetes and maintains a normal blood sugar level in prolonged symmetrical patterns with or without insulin for months. The extract action as shown by the primary, secondary and tertiary extract effects on utilization, the amplitude of the tolerance curves and the depression of the basic glycemia indicates its mode of operation."

Clinics on Secondary Gastro-Intestinal Disorders, Reciprocal Relationships. By Dr Julius Friedenwald, Dr Theodore H Morrison, and Dr Samuel Morrison. Price, \$3. Pp 251. Baltimore. William Wood & Co, 1938.

Symptoms interpreted by the patient as arising within the abdomen, generally in the stomach, occupy a large part of any practitioner's time. That such symptoms may not necessarily indicate a disorder of the organ designated by the patient is not a new idea. Neither is the opposite proposition startling that symptoms may be induced elsewhere than in the gastrointestinal tract by disease of the latter. The attempt of the authors of these clinics has been to systematize and explain the production of gastrointestinal symptoms by disease processes in other parts of the body, and vice versa.

The first clinic contemplates the "relationship of gastrointestinal and cardiac affections." Perhaps the most common abdominal symptom experienced by the patient with cardiac disease is flatulence. Unfortunately this clinic does not do much to enlighten the reader about the origin, or for that matter the dissipation, of the gas. Flatulence is mentioned as a frequent symptom of unrecognized decompensation, but one wonders how frequently physicians of ordinary acuity fail to recognize a failing heart from other evidence than gas. The authors describe cardiac symptoms provoked by gastrointestinal dysfunction, two examples of which are anginal pain and arrhythmia. The type of arrhythmia that may be produced is not mentioned, but it is pointed out (page 9) that gastric stretching "inhibits the action of the vagus and is thus a potent cause of cardiac disturbance."

This is obviously contrary to the usual physiologic and pharmacologic experience and is rather typical of interpretations of neurologic reactions throughout the book. The authors attempt fine distinctions between angina pectoris and a pseudoangina provoked by overeating or eating otherwise indiscreet. It is not suggested, how-

ever, that a heart with incompetent coronary circulation may be incapable of the effort incident to digestion on a large scale. In fact, it is not apparent in the presentation whether the authors think that cardiac symptoms arising from gastrointestinal disturbances, such as gas, occur only in diseased hearts or whether they think such symptoms can be induced as readily in perfectly normal ones. Many cardiologists will argue that cardiac symptoms, for example, angina, dyspnea and arrhythmia, after indiscretions of eating or associated with flatulence, are good evidence of cardiac disease. Several rather frequent sources of cardiac symptoms are not mentioned: esophageal diverticula and diaphragmatic hernias, for instance.

On the other hand, in a clinic on the relations of the stomach and the intestines the authors do much better, threading their way adroitly through the maze of chronic appendicitis, to come out neutral. Curiously they omit any mention of regional enteritis.

The old vagueness recurs in the clinic presenting the endocrinopathies. One is discouraged by the summary of Addison's disease, in which a discussion of the role of hypochloremia and potassium intoxication in the genesis of the typically severe abdominal symptoms is strangely lacking. Really humanitarian work could be done in this field, for on many patients with adrenal insufficiency exploratory procedures are done in the hot summer months for "gall stones," "bowel obstruction" and other conditions.

Perhaps the titling of the book as "Clinics" justified in the authors' minds the dogmatic and occasionally inaccurate presentation. The work fails to fulfil the expectations of the reader who seeks a serious analysis of obscure symptom formation.

Angina Pectoris. Nerve Pathways, Physiology, Symptomatology and Treatment. By Heyman R. Miller, M.D. Price, \$3.25. Pp. 275. Baltimore: The Williams & Wilkins Company, 1939.

This book is primarily intended to present a pictorial representation of the autonomic nervous connections of the human heart. The purpose of these pictures is to make clear the pathways for the radiation of the pain of angina pectoris and the possible sites for a surgical attack on this syndrome. Such a purpose is certainly laudable, and the drawings and their legends are admirably done. Unfortunately, the author has also included a discussion of his conception of the pathogenesis and the therapy of angina pectoris. The author's view of pathogenesis is best quoted from page 7: "We prefer, therefore, to consider angina pectoris a paroxysmal upheaval (of the autonomic nervous system) of central origin, and thus whether the individual has normal or abnormal coronary vessels. Excepting the sequelae of cardiovascular damage, the train of events following a sudden coronary occlusion is but one form of this paroxysmal upheaval." To the reviewer the second sentence cited *implies* that the occlusion of a coronary artery is simply one type of stimulus for the central upheaval. This relationship is not strictly drawn, however, and nowhere else in the book is specific mention made of any other stimulus for this outburst of autonomic activity. Nor is there any clear statement as to whether or not this outburst could be purely of central origin, as is an epileptiform attack. Tacit rejection by the author of a unitary origin for the attack of angina pectoris leads to the frequent, though undefined, use of the terms "coronary angina pectoris" and "noncoronary angina pectoris." This belief in the central origin of the anginal attack is reminiscent of the early views of Laennec and others, views which are usually considered definitely *passé*.

The author's ambivalent thinking is also apparent in the sections devoted to therapeutics. In describing the medical management of an attack of angina pectoris, the author writes as if the attack were due to occlusion of a coronary artery, rather than to a central upheaval. A bizarre group of drugs, 105 in all, is advocated for treatment. In the discussion of the diuretics one finds (page 188): "Some endocrine products are known to possess a diuretic action, the pituitary extracts (0.5-1 cc.) in diabetes insipidus, etc. Their use, however, is quite exceptional." One might even say it is quite *exceptionable*. The author is enthusi-

astic about surgical procedures, particularly those that interrupt the sympathetic nervous connections of the heart. He does not consider the loss of pain as danger signal to be of any consequence, for he thinks that other symptoms of the upheaval of the autonomic system (for example, *angor animi* and sweating) "may carry the same weight as a danger or warning signal."

Cardiovascular Diseases Their Diagnosis and Treatment By David Scherf, M D and Linn J Boyd, M D, F A C P Price, \$6.25 Pp 458
St Louis The C V Mosby Co, 1939

This book covers the most important problems in connection with cardiovascular disease in a more concise form than is usual in standard textbooks. The views expressed are based on the authors' personal experience, and no bibliography is appended. The views are not in discordance with generally accepted trends of thought. Two contributions to the value of the discussions are first, the deliberate attempt to explain the underlying disturbances of physiology responsible for the clinical manifestations encountered in various abnormal cardiovascular states, and, second, the emphasis placed on the evaluation of data acquired at the bedside rather than through instrumental aid—information which might not always be available to every physician.

The initial chapters are devoted to the discussion of the mechanism and the differential diagnosis of dyspnea, as it occurs under various conditions, and of other clinical manifestations of cardiac failure. Special emphasis is devoted to the phenomenon of paroxysmal nocturnal dyspnea.

The remaining chapters deal with the conventional pathologic lesions affecting the heart and the peripheral vascular system, with extracardiac factors which eventuate in cardiopathies and with functional disturbances related to the cardiovascular apparatus. Therapeutic procedures employed in the various fields of cardiovascular disease are discussed in considerable detail. The derivatives of purin receive wide consideration and it is the authors' belief that relatively large doses should be administered in a short period of time in order to achieve satisfactory diuresis in cases of congestive heart failure.

The authors must be complimented on the straightforward manner in which their views are presented. Their book contains much valuable information, and while it is not intended to be a textbook in the ordinary sense of the word it is well worth reading by all who are concerned with the problems of cardiovascular disease.

Letters à un jeune praticien, sur les maladies de l'an us et due rectum By Roger Savignac Preface de Gosset Paper Price, 26 francs Pp 130
Paris Masson & Cie, 1937

The author has had approximately twenty years' experience in the Surgical Clinic of Salpêtrière as a consultant for diseases of the anus and rectum. Personal impressions gained from such clinical experience have been incorporated in this volume.

The importance of the examination of the anus and of the rectum is discussed, with the instruments used and the technic. He believes such an examination is indispensable in certain cases. The discussion of carcinoma of the rectum reveals an attitude of pessimism as to the general prognosis of such a condition. Surgical intervention is mentioned as the only curative form of treatment available. The beneficial effect of radium is mentioned. This phase of the subject is probably not in accordance with certain incorrect views in this country. He correctly emphasizes that roentgen and radium therapy are important methods in the management of carcinoma of the rectum and anus in certain cases.

The letter dealing with *recto-colites graves* discusses the general clinical features of the disease known as chronic ulcerative colitis in this country. A considerable portion of the discussion has to do with medicated instillations in the form of flushes. The discussion of hemorrhoids emphasizes the importance of the injection treatment in the early mild stage of the condition. Treatment of hemor-

rhoids and anal fissure by electrocoagulation seemed to produce satisfactory results in certain cases. There is considerable discussion about the diathermy treatment of rectal stricture.

The book is written in a free, informal style and made up of a series of letters addressed to "my friend." It contains no bibliography or photographs. Such a volume should have a limited appeal, for the remarks are general and detailed discussion has been omitted. It should be read by those who enjoy a general discussion of diseases of the anus and rectum.

Sex and Internal Secretions. A Survey of Recent Research. By Edgar Allen, Charles H. Danforth and Edward A. Doisy, editors. With a foreword by Robert M. Yerkes. Second edition. Price, \$12.00. Pp 1,346, with illustrations. Baltimore: Williams and Wilkins Co., 1939.

The introduction to this volume states that the book deals predominantly with the subject of the mediation, by hormones circulating in the blood, of the sexual characteristics which are especially characteristic of the vertebrates, including man. It is impossible adequately to present a review of this more than 1,300 page book in the form of an abstract, because the editors have painstakingly examined all phases of published work dealing with an increasingly complex subject, and have presented them clearly and with essentially irreducible brevity. Fundamental subjects necessary to complete understanding of the whole subject, such as "cytological and genetic bases of sex," "embryonic development of sex," "modification of development of sex" and "sex and secondary sex characters" are considered in section A, which precedes the chapters dealing with topics perhaps more familiar to the general reader.

The second division of the book is concerned with the physiologic aspects of the sexual glands, germ cells and accessory organs. An example of the comprehensiveness of the book is chapter 8, on the "endocrine function of the ovaries," which consists of 143 pages of discussion based on a bibliography of more than 700 references.

Section C deals with the "biochemistry and assay of gonadal hormones." Section D is on the "hypophysis and the gonadotropic hormones of the blood and urine in relation to the reproductive system."

The concluding chapter contains, among other things, material on the "relation of the vitamins to sex glands."

In this book may be found the careful compilation of data related to the subject that will enable student, teacher and investigator to review thoroughly what is known about sex and internal secretions at the present time.

The General Tissue and Humoral Response to an Avirulent Tubercle Bacillus Including Growth Characteristics of the Organism. By Sol Roy Rosenthal. Paper. Price, \$2.50. Pp 184, with 80 illustrations. Urbana, Ill.: University of Illinois Press, 1938.

This book reports work done on certain phases of growth of B C G and on the response of the tissues and blood of the guinea pig to B C G given by different routes.

The organism was found to have a cycle of growth resembling that previously described for the virulent tubercle bacillus, with passage through a granular phase. There was no reversion to virulent form in this work.

Tissue response was judged by alterations found in the reticuloendothelial system of body organs with sacrifice of the animals at various periods. This response varied from slight swelling of the cells to increase in number and further to grouping of the cells, often in characteristic tubercles. This reaction was limited variously in time and extent and then regressed.

The report is in monographic style and has a good bibliography. The descriptions of tissues are clear and convincing. Repetition of the many complete descriptions of fairly similar content makes for monotony but undoubtedly adds to the factual value of the report. Criticism may be made of the subjective standard of judging the lesser tissue reactions unless sections are described as complete.

unknowns intermingled with controls. Blood cell studies in the guinea pig suffer from the marked normal variability of white cell content.

This thorough type of work supplies needed knowledge of the extensive participation of the reticuloendothelial system in the reactions to B C G. The inference that the reticuloendothelial system reaction is an immune type of response may still be held sub judice.

La médecine d'urgence. Symptômes, diagnostic, traitement immédiat, formulaire. By J Oddo, M D. Seventh edition. Paper. Price, 120 francs. Pp 840. Paris. Gaston Dom & Cie, 1939.

The popularity of this book is indicated by the necessity for the publication of another, the seventh, edition. The original edition appeared in 1910. This edition is similar to the preceding one, although modifications have been made in order to conform with present day ideas concerning physiology, symptoms, signs and treatment of emergency conditions. The major alterations were made in the chapters on acute cardiac insufficiency, epilepsy, hysteria, chronic hepatitis and nephritis. The book still contains many prescriptions which probably have no more effect than placebos. The author continues to use bloodletting in many conditions in which the rationale for this procedure may be questioned. The use of purgatives containing mild mercurous chlorides, even in the presence of uremia due to primary renal disease, is still recommended.

However, in spite of the fact that the reader may not agree with the author in regard to some of the recommended treatment, the book should be helpful in many respects. Such discussions as those of the abnormal physiology, pathogenesis, symptoms and other aspects of disease are brief and clear and should prove of value. The book covers an extensive field and includes most of the conditions that require immediate attention. Therapeutic methods in emergencies have always interested the clinician, while, even more, European ideas of treatment in these emergencies quite often are of particular concern to American clinicians.

The reviewer considers the book worthy of a continued place among the present day clinical books.

Introduction to Ophthalmology. By Peter C Kronfeld, M D, Professor of Ophthalmology, The Peiping Union Medical College. Price, \$3.50. Pp 331, with 37 illustrations. Springfield, Ill. Charles C Thomas, Publisher, 1938.

Kronfeld has made a very valuable contribution to facilitate teaching in ophthalmology. This volume is concise but thorough.

A number of diseases of the eye are not discussed in the general text, but they are described briefly in the index. Details of diagnosis and of examination are not included, instead, the author stresses the physiology and the pathogenesis of the physiologic and pathogenic factors in diseases of the eye. One chapter is an interesting discussion on the physiology of the retinal circulation. Another is a comprehensive survey of the visual pathway. The author stresses the importance of a thorough knowledge of the anatomy in making a differential diagnosis of intracranial lesions.

Principles are stated clearly in a more or less conversational way, making the book differ from the majority of textbooks. The author limits his recommendations for treatment to methods which he considers thoroughly tried. There is a bibliography at the end of each chapter.

This book is highly recommended as an adjunct to any study of ophthalmology.

Anatomic Factors in Hemorrhoids and Varicose Veins of Lower Extremities. By G N Alexandrov. Paper. Price, 27.50 kopecks. Pp 109, with 64 illustrations. Samarxand, 1938.

This little volume is the result of painstaking anatomic postmortem dissections of venous trunks in 30 human cadavers. 20 with hemorrhoids and 10 with varicose veins. The dissections included the sites of dilated veins as well as the pelvic and thoracic veins.

These studies show that the pathologic dilatation of veins is due to a congenital maldevelopment of the venous system, a lack of adequate anastomoses between the three venous systems portal, cava inferior and azygos-hemiazygos. Thus, the real cause of disturbance lies much higher than the site of lesion. This maldevelopment of anastomoses occurs in 3 to 5 per cent of normal people. It is in this group of people that hemorrhoids and varicose veins develop. The malformation can be explained on embryologic and phylogenetic bases.

The illustrations, though quite inexpensively reproduced, are adequate. The literature embraces 119 Russian and 43 European sources. The volume is of considerable interest to an anatomist as well as to an inquisitive surgeon.

Endocrinology in Modern Practice By William Wolf. Second edition. Price, \$10. Pp 1077, with 189 illustrations. Philadelphia W B Saunders Company, 1939.

In a review of the first edition of this book several years ago it was suggested that this was probably the best brief text on endocrinology yet produced. The second edition seems to maintain the same position. Endocrinology is a complex subject in a state of rapid flux. It is practically impossible to cover all its aspects authoritatively or adequately. But a vast amount of useful information is assembled here between two covers, and the illustrations and tables are especially valuable. For the clinician good summaries of anatomic and physiologic observations not readily accessible in most textbooks are assembled. There are some controversial points, especially in connection with current work on pituitary extract and sex hormones, but on the whole this book represents a sound appraisal of the subject.

Medical Jurisprudence and Toxicology By William D McNally. Price, \$3.75. Pp 386, with 37 tables. Philadelphia W B Saunders Company, 1939.

The reviewer is most favorably impressed with this book, which seems to contain within reasonable compass the essential factors of medicolegal medicine. The first sections deal with such matters as signs of death, injuries, gunshot wounds and blood stains. In the later chapters drugs and poisons are discussed. The material is well arranged, and there are many references and an index.

News and Comment

The American College of Physicians—The twenty-fifth annual session of the American College of Physicians will be held in Boston, April 21-25, 1941, with general headquarters at the Statler Hotel.

Dr William B Breed, of Boston, is general chairman of the session and will be in charge of the program of clinics and demonstrations in the hospitals and medical schools and of the panel and round table discussions to be conducted at the headquarters.

OBSERVATIONS ON INDUCED THIAMINE (VITAMIN B₁) DEFICIENCY IN MAN

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Reports of controlled observations on induced thiamine (vitamin B₁) deficiency in human beings have been few,¹ and in only two of these reports^{1c,d} has the restriction of vitamins been limited to thiamine. One of these studies^{1d} was reported by three of us (Williams, Mason and Smith) in December 1939. In that study, 4 young women for twenty-one weeks received a diet which was more deficient in vitamin B₁ than commonly is reported in association with the syndrome of beriberi. This diet was made adequate in vitamin A, ascorbic acid,

From the Rochester State Hospital and the Mayo Foundation

Presented in abstract to the American Institute of Nutrition, New Orleans, March 13, 1940

From the Division of Biochemistry (Dr. Mason), the Mayo Clinic, and from the Departments of Medicine (Dr. Wilder) and of Neurology and Psychiatry (Dr. Smith), the Mayo Foundation

1 (a) Cowgill, G. R. Human Requirements for Vitamin B₁, in *The Vitamins*. A Symposium Arranged Under the Auspices of the Council on Pharmacy and Chemistry and the Council on Foods of the American Medical Association, Chicago, American Medical Association, 1939, chap. 12, pp. 229-248. (b) Elsom, K. O. Experimental Study of Clinical Vitamin B Deficiency, *J. Clin. Investigation* **14**: 40-51 (Jan.) 1935. (c) Jolliffe, N., Goodhart, R., Gennis, J., and Cline, J. K. The Experimental Production of Vitamin B₁ Deficiency in Normal Subjects. The Dependence of the Urinary Excretion of Thiamin on the Dietary Intake of Vitamin B₁, *Am. J. M. Sc.* **198**: 198-211 (Aug.) 1939. (d) Williams, R. D., Mason, H. L., and Smith, B. F. Induced Vitamin B₁ Deficiency in Human Subjects, *Proc. Staff Meet., Mayo Clin.* **14**: 787-793 (Dec. 13) 1939. (e) Elsom, K. O., Lukens, F. D. W., Montgomery, E. H., and Jonas, L. Metabolic Disturbances in Experimental Human Vitamin B Deficiency, *J. Clin. Investigation* **19**: 153-161 (Jan.) 1940.

proteins and minerals and in addition was supplemented with crystalline preparations of riboflavin and nicotinic acid. The delayed development of symptoms and failure of the subjects to show the classic signs of beriberi prompted repetition of the study with other subjects. Also it seemed desirable to provide more adequately for the factors of the vitamin B complex other than thiamine. For this purpose autoclaved yeast was given instead of crystalline riboflavin and nicotinic acid.

PROCEDURE

Six white women, patients of the Rochester State Hospital, were chosen on the basis of their voluntary cooperation, absence of physical defects,² absence of any history of abnormal nutrition and quiescence of associated mental illness. These women were active physically and were engaged in hospital housework. The group included asthenic and sthenic, hyperkinetic and sedentary, thin and well nourished women. Their ages ranged from 21 to 46 years and their weights from 50 to 65 Kg.

A basal diet was arranged to provide not more than 150 micrograms (0.15 mg) of thiamine (that is, 50 international units of vitamin B₁) daily. The diet was composed of white flour, sugar, tapioca, corn starch, washed polished rice, white raisins, egg white, cottage cheese, butter, hydrogenated fat, black tea and cocoa. Many samples of each of these foods were analyzed for their content of thiamine, and in the calculations of intake of thiamine the highest analytic values were used. These analyses were by the method of Hennessy and Cerecedo.³ The allowance of carbohydrate was never less than 175 Gm, and, in addition, sugar, candies and fat were permitted ad libitum. There was not more than 0.08 microgram of thiamine to each calory in the diet and 0.12 microgram of thiamine to each nonfat calory. The allowance of protein was well above the minimal requirement, although, because many foods rich in protein are carriers of thiamine, the variety of such foods was necessarily limited. The diet was supplemented with 20 Gm of autoclaved brewers' yeast (containing only 8 micrograms of thiamine), 50 mg of crystalline ascorbic acid, halibut liver oil in an amount to provide 8,000 units of vitamin A, iron and calcium.

The urine was analyzed for thiamine at intervals not less frequent than once weekly. The analytic method of Hennessy and Cerecedo was used for this purpose. These analyses served as a suggestive index of the degree of thiamine deprivation and provided a check or control for the intake of thiamine. Body weight, physical and neurologic signs and symptoms, tolerance for exercise, electrocardiographic changes, size of the heart as determined by roentgen examination, gastric analysis, dextrose tolerance, blood counts, blood sugar, plasma protein, blood content of bisulfite-binding substances and lactic acid (before and after exercise) and basal metabolic rates were determined at intervals during the period of deprivation of thiamine and again in a subsequent period, when thiamine was administered. Gastrointestinal motility as evidenced by roentgen examination after a barium

2 Except in case 3, in which deformity of the left leg was present owing to anterior poliomyelitis during childhood.

3 Hennessy, D. J., and Cerecedo, L. R. The Determination of Free and Phosphorylated Thiamin by a Modified Thiochrome Assay, *J. Am. Chem. Soc.* 61: 179-183 (Jan.) 1939.

sulfate meal was studied at the end of the period of restriction of thiamine and again during the following period, when thiamine was administered

Needless to say, the carrying out of observations of this nature entailed unusual cooperation of nursing and dietary assistants ⁴

OBSERVATIONS ON SUBJECTS WHILE THEY WERE RECEIVING THE DIET DEFICIENT IN THIAMINE

The period of restricted intake of thiamine extended from Dec 12, 1939 to March 9, 1940 (eighty-eight days) The more conspicuous signs and symptoms observed during the period of inadequate intake of thiamine are presented in table 1 It can be seen that the amount of thiamine excreted in the urine fell rapidly to remarkably low values The time of onset of signs and symptoms varied In general, the more active subjects were the first to experience symptoms The abnormalities ultimately noted in all of the subjects who were deprived of thiamine for periods of several weeks were depressed mental states, generalized weakness, dizziness, backache, soreness of muscles, palpitation, dyspnea and precordial distress (pseudoangina) on exertion, insomnia, anorexia, nausea, vomiting, loss of weight, atony of muscles, very slight roughness of the skin, faint heart sounds, lowered blood pressure and bradycardia when at rest, with tachycardia and sinus arrhythmia on exertion In all cases physical activity greatly decreased Less regularly there were observed states of apathy, reawakening of psychotic trends, difficulty of thought and memory, photophobia, headache, abdominal distention, sensations of cold and heat, burning of the soles of the feet, numbness of the legs, fatigue of the ocular muscles, tenderness of the muscles of the calves and depressed tendon reflexes Changes in the size of the heart were not detectable in any case Edema was not apparent in any case The concentration of plasma proteins remained within normal limits in all cases The values for serum calcium and serum phosphorus remained normal Anemia did not develop, cheilosis was not seen, and there was no reddening of the skin or of the tongue

In all cases the capacity for work, as measured with a calibrated chest weight exercising machine, fell progressively during the period of restricted intake of thiamine (fig 1) Electrocardiographic abnormalities developed They consisted of diminution in the amplitude of all complexes and particularly of the T waves of the chest leads In certain instances the T waves became isoelectric or shallowly inverted (fig 2) In each case the apex of the heart was located by palpation and fluoroscopic examination, and the position for application of electrodes was made the same in all examinations The records were taken

⁴ This work was made possible by the assistance of Miss Phyllis Newman and Miss Margaret Pewters

TABLE 1—Summary of Intake of Food, Intake and Excretion of Thiamine, and More Evident Signs and Symptoms During Period of Restricted Intake of Thiamine

Case	Sex	Age, Years	Height, Cm	Period of Diet	Diet				Thiamine in Urine, Micro grams	Body Weight, Kilo grams	Symptoms
					Carbo hydrate, Gm	Pro tein, Gm	Fat, Gm	Calories			
1	Female	23	163	Nov 27 to Dec 7, 1939	261	65	111	2,303	750	320	54.5
				Dec 8, 1939 to Jan 12, 1940	275	56	59	1,855	110	21	54.5
				Jan 13 to Feb 12, 1940	271	57	60	1,532	145	16	53.7
				Feb 13 to March 8, 1940	217	39	49	1,465	121	23	51.4
											Asymptomatic on preliminary observation
2	Female	46	161	Nov 27 to Dec 7, 1939	260	65	108	2,272	750	98	55.5
				Dec 8, 1939 to Jan 12, 1940	247	55	57	1,721	139	17	55.5
				Jan 13 to Feb 12, 1940	186	43	53	1,393	119	15	50.0
				Feb 13 to March 8, 1940	200	32	37	1,261	95	13	45.6
											Asymptomatic on preliminary observation
3	Female	26	159	Nov 27 to Dec 12, 1939	274	64	111	2,351	750	68	64.5
				Dec 13, 1939 to Jan 12, 1940	284	52	58	1,866	137	10	66.4
				Jan 13 to Feb 12, 1940	224	44	53	1,549	122	14	64.5
				Feb 13 to March 8, 1940	213	38	48	1,436	107	15	62.7
											Asymptomatic on preliminary observation
4	Female	33	155	Nov 27 to Dec 12, 1939	274	64	111	2,462	750	124	50.0
				Dec 13, 1939 to Jan 12, 1940	322	59	59	2,075	119	12	49.2
				Jan 13 to Feb 12, 1940	215	40	48	1,452	113	10	46.5
				Feb 13 to March 8, 1940	176	22	28	1,044	73	14	41.8
											Asymptomatic on preliminary observation

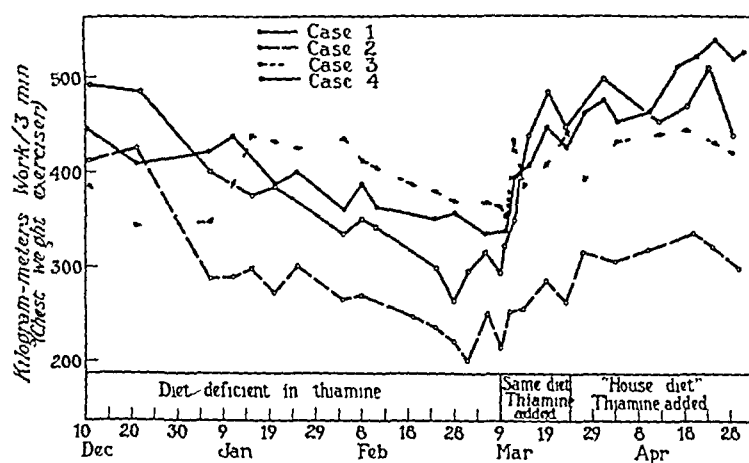


Fig 1—Capacity of subjects for work, as measured by a calibrated chest weight exerciser, during the period of restricted intake of thiamine (Dec 12, 1939 to March 8, 1940) and during the subsequent period in which the restricted diet was supplemented with thiamine hydrochloride (March 9 to 26, 1940)

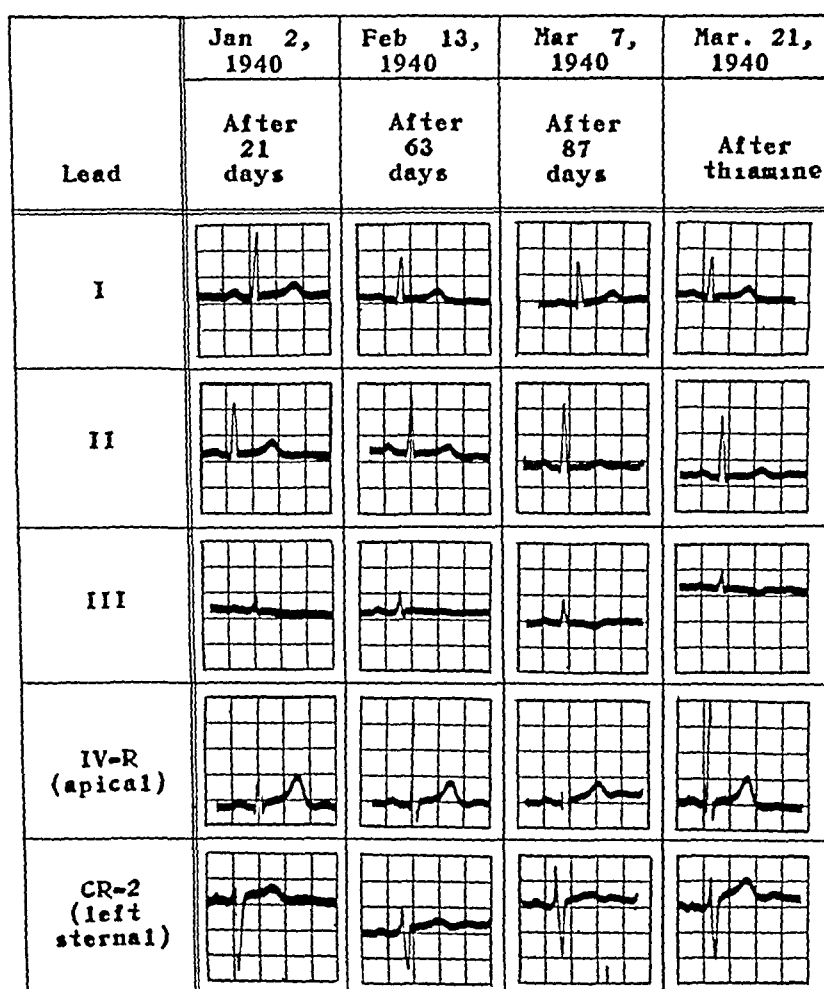


Fig 2—Electrocardiographic changes in the period of restriction of thiamine and after thiamine was given

with the subject in the recumbent position. In 3 of the 4 subjects who received the diet low in thiamine for prolonged periods, blood sugar (method of Miller and Van Slyke⁵) time curves became diabetic in type (fig 3), and values for the concentration of bisulfite-binding substances in the blood (method of Clift and Cook⁶) and for lactic acid (method of Miller and Muntz⁷) in the blood were elevated irregularly before, but particularly after, exercise (fig 4). In all cases gastric acidity, as determined by a test meal of 100 cc of 7 per cent solution of alcohol, was decreased, and gastrointestinal motility as evidenced by roentgen examination after a barium meal was impaired (fig 5).

The period of restricted intake of thiamine was terminated after eighty-eight days (March 9, 1940) by giving a subcutaneous injection of 1 mg of thiamine hydrochloride. The diet low in vitamin B₁ was

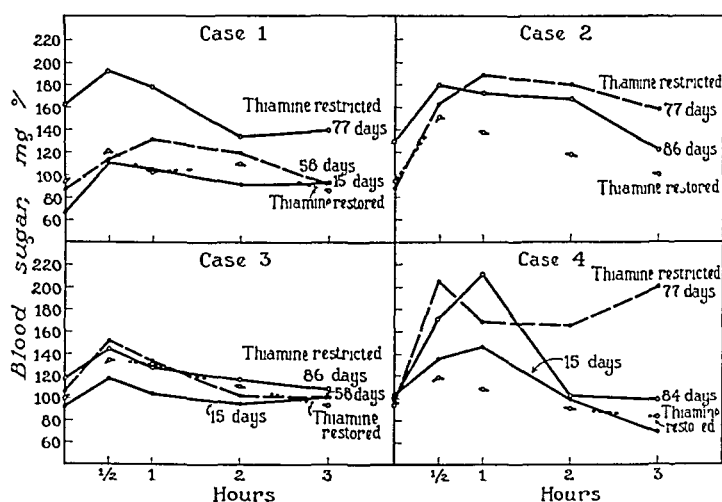


Fig 3—Blood sugar time curves during the period of restricted intake of thiamine (Dec 12, 1939 to March 8, 1940) and again during the period in which the restricted diet was supplemented with thiamine hydrochloride (March 9 to 26, 1940)

continued until March 26. During the interval from March 9 to March 15 daily injections of small doses of thiamine hydrochloride were made, and the amount of thiamine contained in the urine was determined daily.

Subjective improvement was observable in every case within a few hours after the initial injection of 1 mg of thiamine hydrochloride. Nausea and vomiting ceased, food which previously had been revolting

5 Miller, B F, and Van Slyke, D D. A Direct Microtitration Method for Blood Sugar, *J Biol Chem* **114** 583-595 (July) 1936.

6 Clift, F P, and Cook, R P. A Method for Determination of Some Biologically Important Aldehydes and Ketones, with Special Reference to Pyruvic Acid and Methylglyoxal, *Biochem J* **26** 1788-1799, 1932.

7 Miller, B F, and Muntz, J A. A Method for the Estimation of Ultra-microquantities of Lactic Acid, *J Biol Chem* **126** 413-421 (Nov) 1938.

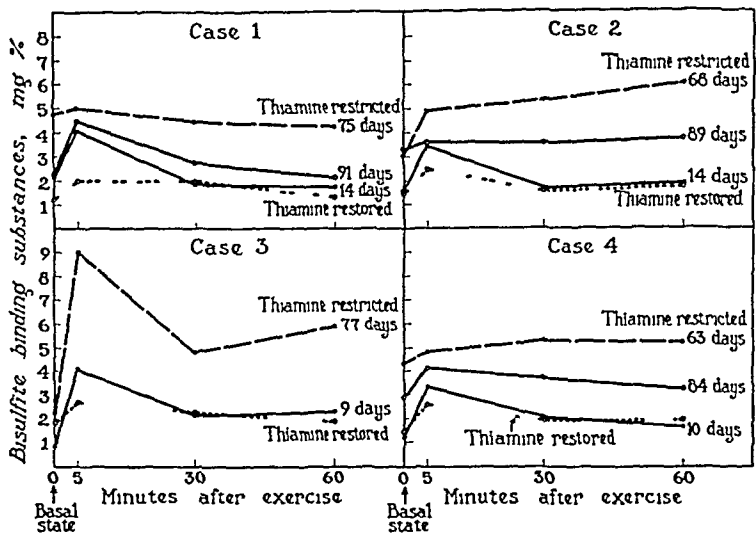


Fig 4—Values of bisulfite-binding substances in the blood under basal conditions and at intervals after one minute of vigorous exercise, during the period of restricted intake of thiamine (Dec 12, 1939 to March 8, 1940) and again during the period in which the restricted diet was supplemented with thiamine hydrochloride (March 9 to 26, 1940)

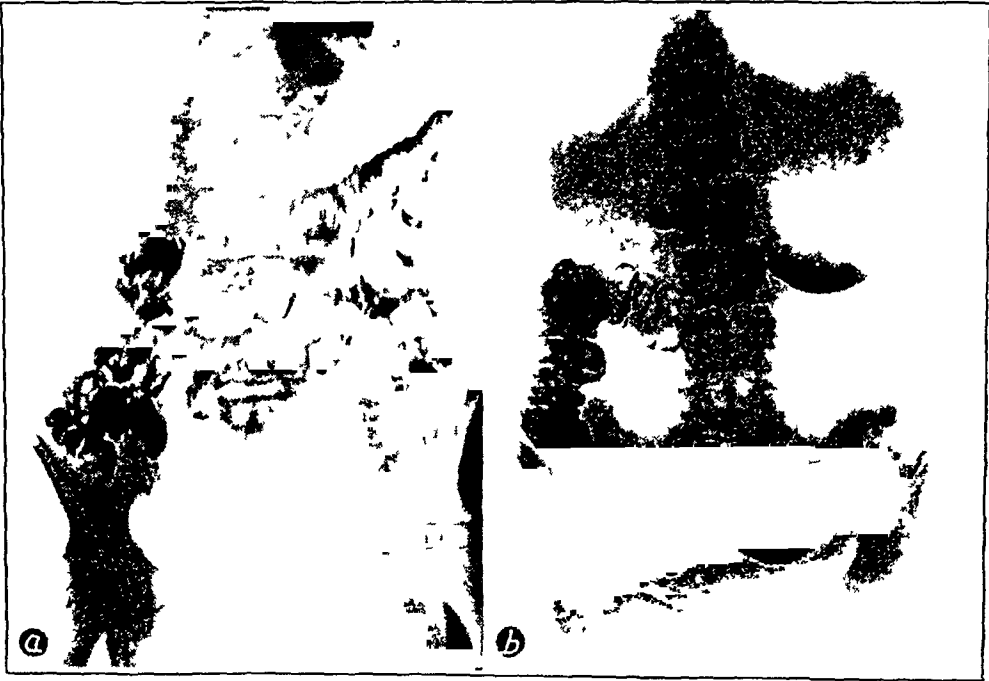


Fig 5—Roentgen evidence of impaired gastrointestinal motility (case 4) three hours after plain barium sulfate meals. Roentgenogram *a* was made March 8, 1940, after a period of restriction of intake of vitamin B₁ (Dec 12, 1939 to March 8, 1940), roentgenogram *b* was made March 22, 1940, in a period (March 9 to 26) in which the patient was receiving a dietary regimen restricted in vitamin B₁ content and supplemented with thiamine hydrochloride.

to the patient was eaten without urging, fatigue disappeared, activity was resumed, and apathy was replaced by lively interest in ward work and current events. During the eighteen days (March 9 to 26 inclusive) in which administration of thiamine hydrochloride represented the only change made, all signs and symptoms incident to the period of restriction of thiamine disappeared. The electrocardiograms became normal, the previously diabetic type of sugar tolerance curve was replaced by a normal curve, previously abnormal values for bisulfite-binding substances and lactic acid were replaced by normal values, and the previously sluggish motility of the intestinal tract was replaced by normal activity. In case 1, however, depressed tendon reflexes and weakness of the muscles of the calves persisted in a diminishing degree for several weeks.

OBSERVATIONS ON SUBJECTS DURING ADMINISTRATION OF A DIET
DEFICIENT IN THIAMINE, SUPPLEMENTED WITH
THIAMINE CHLORIDE

Two of the 6 subjects placed on the diet restricted in thiamine (cases 5 and 6) were given thiamine hydrochloride orally. This was done without their knowledge. The basal diet contained 0.15 mg of thiamine. The initial dose of thiamine hydrochloride was 0.5 mg. It was given eleven days after starting the diet, at a time when the urinary content of thiamine had fallen to very low levels. Thereafter a daily dose of thiamine hydrochloride was administered in gradually increasing doses up to 2 mg a day (table 2). A substantial increase of thiamine in the urine did not occur until the intake of the vitamin had reached 0.95 mg. Marked improvement in the clinical state of the subject was accompanied with an increased capacity for work (fig. 6). On March 27, when the daily level of intake was lowered from 2 mg to 0.75 mg, the capacity for work again fell, and when more thiamine was given, on April 10, the capacity for work again increased.

In both of these subjects an intake of less than 0.95 mg of thiamine daily was associated with fatigue, irritability, poor appetite, insomnia, soreness of muscles and constipation. On the other hand, a feeling of unusual well-being associated with unusual stamina and enterprise accompanied the period (March 7 to 26) in which the intake of thiamine was at the level of 2 mg daily. This was followed by a letdown when the intake of thiamine was lowered by substituting the routine hospital diet for the basal diet which had been supplemented with thiamine hydrochloride. The change at this time was so striking that 1 subject begged to be returned to the basal diet. During the period when the subjects were receiving the basal diet supplemented with less than 0.80 mg of thiamine hydrochloride the electrocardiograms were slightly

abnormal The abnormality consisted of diminution in the amplitude of the T waves of the left sternal lead (C R-2) The same abnormality was not observable in subsequent tracings (fig 7) The blood sugar

TABLE 2—*Data on Subjects Who Received the Thiamine-Deficient Diet, Supplemented with Thiamine Hydrochloride*

Case, Sex	Age, Height, Cm	Period of Diet	Diet				Thiamine			Body Weight, Kilo grams
			Carbo hydrate, Gm	Pro tein, Gm	Fat, Gm	Calories	Food, Micro grams	Solution, Micro grams	Urine Micro-grams	
5 Female	42 yr 152.5	Nov 27 to Dec 7, 1939	260	65	111	2,300	750		185	51.0
		Dec 8 to Dec 17, 1939	297	56	57	1,925	152		37	51.5
		Dec 18, 1939 to Jan 13, 1940	267	55	58	1,810	140	500	30	53.7
		Jan 14 to Jan 23, 1940	286	60	61	1,933	150	600	36	52.4
		Jan 24 to Feb 5, 1940	277	56	59	1,863	143	700	57	52.8
		Feb 6 to Feb 15, 1940	313	62	62	2,058	158	800	90	52.8
		Feb 16 to Feb 20, 1940	275	58	60	1,872	155	900	120	52.4
		Feb 21 to March 7, 1940	267	52	59	1,807	135	1,000	212	52.0
		March 8 to March 26, 1940	274	53	59	1,839	146	2,000	562	52.8
		March 27 to April 9, 1940	260	65	111	2,300	750		132	54.3
6 Female	28 yr 154	Nov 27 to Dec 7, 1939	254	64	108	2,244	708		117	51.0
		Dec 8 to Dec 17, 1939	273	54	58	1,830	134		20	50.1
		Dec 18, 1939 to Jan 13, 1940	242	56	60	1,732	142	500	28	51.0
		Jan 14 to Jan 23, 1940	313	64	61	2,057	156	600	30	49.7
		Jan 24 to Feb 5, 1940	297	58	59	1,951	150	700	60	49.6
		Feb 6 to Feb 15, 1940	267	53	57	1,793	144	800	64	48.5
		Feb 16 to Feb 20, 1940	234	47	55	1,619	126	900	83	49.2
		Feb 21 to March 7, 1940	289	54	58	1,894	141	1,000	97	48.3
		March 8 to March 26, 1940	258	48	58	1,746	132	2,000	507	48.3
		March 27 to April 9, 1940	232	60	108	2,140	684		60	49.7

time curves and the curves for the concentration of bisulfite-binding substances and of lactic acid after exercise showed no unusual features in these cases

In case 5 a minimal degree of papilledema was noted at a time when the intake of thiamine was restricted. It disappeared later, when the intake of thiamine had been increased to 0.85 mg daily. This recalls

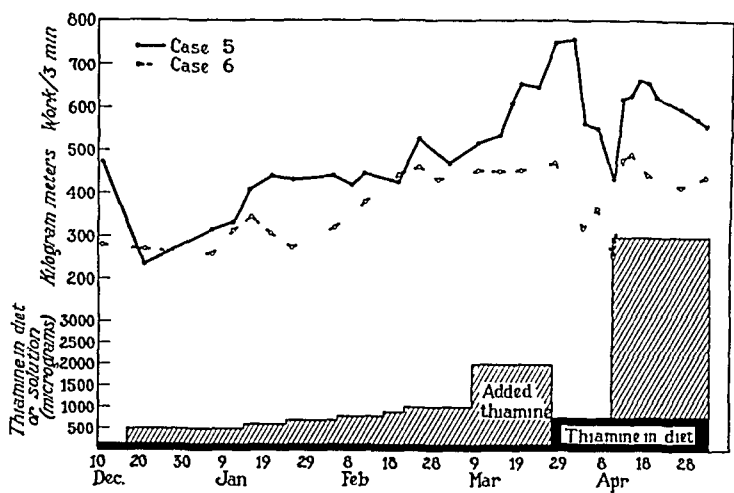


Fig 6—Capacity for work, as measured by a calibrated chest weight exerciser, of subjects receiving the thiamine-deficient diet, supplemented with varying amounts of thiamine hydrochloride

	Case 5		Case 6	
	Feb. 13, 1940 0.95 mg. of thiamine	Mar. 21, 1940 2.15 mg. of thiamine	Jan. 2, 1940 0.64 mg. of thiamine	Mar. 21, 1940 2.15 mg. of thiamine
Lead				
I				
II				
III				
IV-R (apical)				
CR-2 (left sternal)				

Fig 7—Electrocardiographic changes in the period in which the thiamine-deficient diet was supplemented with thiamine hydrochloride

the observation of papilledema in cases of neuritis axialis reported by Kagawa⁸ An instance of papilledema in a patient with pellagra and associated evidence of thiamine deficiency was called to the attention of one of us (Wilder) during a recent visit to the nutrition clinic of the Hillman Hospital in Birmingham, Ala

COMMENT

Observations previously reported by three of us (Williams, Mason and Smith) are confirmed by the results of the work described here, in which 6 subjects for eighty-eight days received a diet which provided daily less than 0.15 mg of thiamine (50 international units of vitamin B₁) but which otherwise was adequate nutritionally After eleven days 2 of these subjects were given thiamine hydrochloride orally, without their knowledge, in gradually increasing daily doses The 4 subjects who obtained no supplementary thiamine experienced striking evidences of nutritional deficiency The 2 subjects whose diets were supplemented with thiamine also revealed evidences of deficiency until their total intake of the vitamin reached 0.95 mg daily From then on they were free from symptoms and performed as effectively on a chest weight exercise machine as at the start of the observations This provided a control of the adequacy of the basal diet in factors other than thiamine However, with further increases in the allowance of thiamine they improved still more, and when the intake reached 2 mg a day they were strikingly more alert and attentive, and their performance with the chest weight exercise was much more satisfactory than it had been originally (fig 6) At the end, when the intake of thiamine was lowered by a return to the routine hospital diet, well-being, alertness and work performance fell again to what they had been originally This constitutes strong evidence that the institutional diet, which by calculation contained approximately 0.6 to 0.8 mg of thiamine daily, provided less than an optimal allowance of thiamine The food in this hospital compares favorably, in our opinion, with that in most institutions Therefore, the observations indicate that institutional diets in general may be subject to criticism on the score of providing less thiamine than is desirable

Another conclusion suggested by our observations is that the isolated withdrawal of thiamine from the diet does not produce beriberi In the earlier study^{1a} 4 subjects were given food that contained less than 0.155 mg of thiamine per day for one hundred and forty-seven days, and in the study which we now are reporting 4 other subjects received a diet that provided less than 0.15 mg for eighty-eight days Yet in

⁸ Kagawa, S Studies on the Relation of Neuritis Axialis to Beriberi in Japan, *Jap J M Sc*, VIII, *Int Med, Pediat & Psychiat* 5:1-60 (Dec) 1938

both studies, edema, which is said to develop in at least one third of all cases of beriberi, cardiac dilatation, which is a common occurrence with beriberi, and neuritic pain, which is regarded as a conspicuous feature of beriberi, were absent. Tenderness of the muscles of the calves, which in no case was severe, paresthesia of the feet and legs, which never was more than mild, and diminution of tendon reflexes were observed, although not with any regularity, and pain was not present in any degree. Thus we are led to question whether thiamine is the vitamin the lack of which is responsible for the classic features of beriberi and to suggest that deficiency of factors of the vitamin B complex other than thiamine may be more important in the production of such features than thiamine itself.

We nevertheless are impressed by the degree of debility induced by the isolated withdrawal of thiamine. Fatigue, lassitude and loss of interest in food developed early and increased progressively as the period of deficiency extended, to the point of intolerance for food. So great was this intolerance that uncontrollable vomiting, even after tube feeding and parenteral injection of solutions of sodium chloride and dextrose, automatically brought the observations to a close. The time of development of symptoms and the time of development of severe symptoms differed among the subjects and seemed to be related to physical activity. The subjects who were more active showed symptoms earlier and were more seriously affected later than others who from the beginning were less energetic. In part, also, a seasonal influence may have been manifest. The period of restriction of thiamine in the earlier study began April 4, 1939, and was continued until August 30 (one hundred and forty-seven days) before the severity of anorexia and vomiting necessitated its termination. In the study reported here the period of restriction of thiamine began Dec 12, 1939 and was continued only until March 9, 1940 (eighty-eight days) before vomiting became equally disturbing. Furthermore, none of the 4 subjects of the earlier study revealed any clear evidence of deficiency until after four or five weeks of restricted intake of thiamine, whereas all 6 subjects of the present study experienced symptoms within ten to fourteen days. The difference was striking. It suggests that a greater total metabolism provoked by low temperature or changeableness of the weather led to a relatively greater requirement for thiamine in the period of the second study.

The disease induced by the isolated restriction of thiamine resembles minutely that disorder which the discriminating psychiatrist designates as neurasthenia. It differs from hysteria, obsessive and compulsive states, anxiety neurosis and other conditions which an indiscriminating physician commonly would lump together with neurasthenia under such designations as chronic nervous exhaustion or functional neurosis. Thus,

neurasthenia, properly defined, may be less of a functional abnormality than has been supposed, and it may depend on improper nutrition of the neurons

The force of this suggestion can be appreciated best by comparing the symptoms and objective evidences of abnormality which we encountered in our studies with the symptoms and abnormalities associated with neurasthenia as recorded by Wilson⁹ The following paragraphs are quoted from him The italics have been employed by us to indicate the symptoms which we encountered in cases of induced deficiency of thiamine

General Symptoms—*Fatigue*, often present on slight exertion and may be curiously selective, in that it is chiefly manifested when the patient's interest is at a low ebb *Loss of weight*, usually dependent on appetite failure

Local Symptoms—*Alimentary* *Capricious appetite*, *anorexia*, *indigestion*, *distension*, *eructation*, *nausea*, *vomiting*, *constipation* or *diarrhea*, *mucous colitis* *Circulatory* Varying degrees of cardiac discomfort, *tachycardia*, *palpitation*, *pseudoanginal sensations*, *heart irregularity* *Vasomotor* *Pallor*, blushing, sweating, *coldness*, *heat* and numerous other phenomena *Genito-urinary* Impotence, nocturnal emissions, genito-urinary paresthesias, *dysmenorrhea*, *dyspareunia*, *frequency of micturition*, increased urinary output, "loose kidneys" *Respiratory system* *Frequent "colds," shortness of breath*, sometimes hastened respiratory rate with shallow breathing *Nervous system* *Peculiar sensations in head* and in fact in every portion of the body, feelings of swelling of the scalp, *band around head*, bursting and stuffiness of head, *headache*, *especially in occipital region*, *peculiar, uncomfortable* or *painful sensations in the abdomen, rectum* or breasts An almost universal complaint is *backache* *Giddiness and dizziness* are common and *insomnia* is rarely absent There may be *photophobia*, *muscae volitantes*, and *eye muscle fatigue*, ear noises, intolerance of ordinary sounds *Mental symptoms* *Inability to concentrate*, *uncertain memory*, *fear of insanity*, *awkwardness* and *self-consciousness* in the presence of others, feelings of inferiority, *irritability*, *depression*, *phobias*, *anxieties*

Not every symptom of neurasthenia was represented in every one of our subjects, but neither is this true of all patients who have neurasthenia We observed tachycardia only when the patient excited herself When she was at rest the pulse was slower than normal, this also is common in cases of neurasthenia Achlorhydria or hypochlorhydria, which was constant in our subjects in the period when thiamine was restricted, is likewise a frequent accompaniment of neurasthenia Constipation became the rule in our subjects, diarrhea was infrequent or transient Possibly long-continued use of cathartics accounts for the diarrhea and the "mucous colitis" that are frequently encountered among patients who have neurasthenia An explanation for the constipation was

⁹ Wilson, G Neurasthenia, in Musser, J H Internal Medicine Its Theory and Practice in Contributions by American Authors, ed 3, Philadelphia, Lea & Febiger, 1938, p 1235

found in the slow emptying of the stomach and the sluggish motility of the intestine. These were observed roentgenologically after a barium sulfate meal during the period of deficient intake of thiamine but not after administration of thiamine hydrochloride. The roentgenologist commonly lays little stress on delayed passage of barium through a bowel which otherwise reveals no abnormalities, and we are led to suspect that he thereby may be overlooking cases of thiamine deficiency. Similarly, the cardiologist commonly disregards electrocardiograms that show only diminished amplitude of T waves, yet with our subjects this abnormality first appeared when they were deprived of thiamine, it remained week after week during the period of restriction and was rapidly corrected afterward, when thiamine hydrochloride was administered (fig 2).

At the end of the period of deprivation of thiamine, the clinical picture presented in all our cases was that of anorexia nervosa, and this condition as one encounters it clinically is usually an end stage of more severe neurasthenia. We wish to make clear, however, that we are comparing the state of thiamine deficiency not with the functional neuroses in general but with neurasthenia (when the term "neurasthenia," is used with the discrimination that we have demanded). Nor do we mean to imply that all patients with conditions diagnosed as neurasthenia could be shown to be victims of thiamine deficiency, especially of a primary deficiency of this vitamin. Possibly only a small percentage of such conditions are nutritional in origin, but it may be that the number is large. What we do suggest, on the basis of observations of the disease induced by withdrawal of thiamine, is that thiamine deficiency, as it exists in this part of the United States, where one observes only a few cases of beriberi or pellagra, should be looked for principally in that large group of patients who have the infirmity to which the diagnosis neurasthenia has appropriately been applied.

McLester¹⁰ has called attention to the similarity of the so-called prepellagrous state and neurasthenia. He wrote

Since J. B. McLester in his study of the histories of pellagrins seen at the Hillman Hospital in Birmingham made the significant discovery that an appreciable number of these patients had been admitted the previous year under the diagnosis of neurasthenia, we have made an effort toward the early recognition of such cases of subclinical pellagra. Many of the patients recently studied could with some justice be called neurasthenic, but when given nicotinic acid and thiamin, with a diet appropriate for pellagra, they recovered their nervous stability and sense of well-being to a remarkable degree. I believe that with a good history, the prepellagrous state can be recognized without great difficulty and further progress of the disease stopped.

10 McLester, J. S. Borderline States of Nutritive Failure, *J. A. M. A.* 112:2110-2114 (May 27) 1939.

It now is well recognized that few cases of pellagra depend exclusively on the presence of a deficiency of nicotinic acid and that deficiency of thiamine is evident in most such cases. It is not improbable that many of the nervous and mental symptoms of pellagra depend primarily on the lack of sufficient thiamine in the dietary regimen.

CONCLUSIONS

1 A dietary supply of 0.95 mg of thiamine (285 international units of vitamin B₁) was associated with no clear evidence of nutritional deficiency, but it provided less than a sufficient amount of this vitamin for the best nutritional state of the patient.

2 A climatologic factor may influence the rate of development of evidence of thiamine deficiency. A diet restricted to 0.15 mg of thiamine (50 international units of vitamin B₁) was tolerated for one hundred and forty-seven days by 4 subjects who received it during the summer months. A similar diet given to 4 other subjects in the winter months could be tolerated for only eighty-eight days. Symptoms of thiamine deficiency developed earlier among the subjects whose diets were restricted during the winter months.

3 Physical activity affects the rate of development of evidence of thiamine deficiency. When diets were restricted to 0.15 mg of thiamine, subjects who were more active experienced symptoms earlier and were more seriously affected later than those who were less active. The shortest time for the appearance of clear evidence of deficiency was twelve days, the longest, forty-eight days.

4 The disease induced by restricting the intake of thiamine differed from classic beriberi in that edema, cardiac dilatation and peripheral pain were absent. We are led to question whether thiamine is the vitamin the lack of which is responsible for these classic features of beriberi.

5 The early stage of the disease induced by restricting the intake of thiamine closely resembles neurasthenia, the later stage simulates anorexia nervosa. Therefore, we propose that states of thiamine deficiency, as these exist in our part of the country, where few cases of beriberi or pellagra are encountered, should be looked for principally in cases in which the diagnosis neurasthenia has appropriately been made.

PAIN IN THE SHOULDER AS A SEQUEL TO MYOCARDIAL INFARCTION

A CARLTON ERNSTENE, M D
AND
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CLEVELAND

The development of persistent pain in the shoulder region in patients who have disease of the coronary arteries is sufficiently common to warrant more comment than it has hitherto received. The mechanism responsible for the pain has not been determined, but the frequency of its occurrence is such as to indicate more than a chance relationship to the attendant heart disease. The pain occurs most commonly as an aftermath of myocardial infarction, but it also develops at times in persons who have frequent and severe attacks of angina pectoris and who present no evidence of having suffered from earlier coronary occlusion. One or both shoulders may be affected, but the left shoulder is more commonly involved than the right. The pain lasts for several weeks or months and is usually increased by movement of the arm but is not influenced by walking. In patients who experience attacks of angina pectoris after coronary occlusion, the pain may be greatly increased during, and for some time after, the anginal seizures. Examination of the involved shoulder usually reveals limitation of movement, especially of abduction and external rotation, with tenderness about the joint or over the lateral aspect of the upper part of the arm. The common clinical picture is thus identical with that of peri-arthritis of the shoulder. At times, however, pain and a sensation of weakness are the only symptoms, there is no appreciable limitation of motion and no tenderness can be elicited by firm pressure. In a certain number of patients, also, changes similar to those of rheumatoid arthritis develop in other joints either simultaneously with or subsequent to the appearance of the symptoms in the shoulder.

MATERIAL AND RESULTS

The present report is based on a study of 17 cases of persistent pain in the shoulder region encountered in a series of 133 consecutive cases of myocardial infarction (table). In 3 patients the pain in the shoulder

Read before the American Clinical and Climatological Association, Saranac Lake, N. Y., Oct. 10, 1939.

Pain in the Shoulder as a Sequel to Myocardial Infarction

Case No	Sex	Age	Shoulder Affected by Radiation of Cardiac Pain	Location of Infarct	Shoulder Affected	Interval Between Coronary Occlusion and Onset of Persistent Pain in Shoulder	Duration of Pain in Shoulder	Angina Pectoris After Coronary Occlusion	Comments
1	M	40	0	Anterior	Left, right later	Left shoulder 5 months, right shoulder 9 months	8 months	0	Typical periarthrititis
2	F	58	Left	?	Left	Coincident	3 months	+	Typical periarthrititis
3	M	60	Left	Anterior	Left	Coincident	19 months	+	No limitation of movement
4	M	49	Right	Posterior	Both	3 months	18 months improved	+	Periarthritis simultaneous development of rheumatoid arthritis involving fingers and knees
5	M	64	0	Anterior	Left	3 months	3 months unimproved	+	No limitation of movement
6	F	49	Left	Anterior	Right, left later	Right shoulder 4 months, left shoulder 7 months	9 months	0	Periarthritis, rheumatoid arthritis involving elbows, wrists, fingers and knees developed simultaneously with pain in right shoulder
7	M	57	Both	Anterior	Right	3 weeks	4 months	0	Typical periarthrititis, later rheumatoid arthritis
8	M	65	Left	Anterior	Left	1 week	10 weeks	0	Persistent pain in left shoulder and left scapular region without limitation of movement
9	F	49	Left	Posterior	Left	Coincident	4 months unimproved	0	Mild periarthrititis, associated numbness and weakness of left arm
10	M	49	Left	Anterior	Left	2 months	9 months	0	Mild periarthrititis, simultaneous development of rheumatoid arthritis involving fingers
11	M	40	0	Anterior	Left	12 months	7 months unimproved	+	No limitation of movement
12	M	57	Left	Anterior	Left	18 months	3 months improved	+	No limitation of movement, in addition to painful shoulder, residual numbness and swelling of left hand after anginal attacks
13	M	76	Both	Anterior	Right	22 months	6 months improved	+	Periarthritis, simultaneous development of rheumatoid arthritis involving wrists and fingers
14	M	47	0	Posterior	Left	5 years	4 months	+	Typical periarthrititis
15	M	59	0	Posterior	Both	8 years	9 months	+	Typical periarthrititis
16	M	55	Left	Anterior	Both	See comment	6 months unimproved	+	Angina pectoris and persistent pain in shoulder for 1½ years before coronary occlusion, worse after occlusion
17	F	53	Both	Anterior	Both	See comment	2 years unimproved	+	Rheumatoid arthritis and persistent pain in shoulder for 6 years before coronary occlusion, pain in shoulder worse after occlusion

dated from the attack of coronary occlusion, and in 7 others it developed within five months after the attack. In 5 patients the pain did not appear until one to eight years after the coronary accident, but it is worthy of note that all of these patients had experienced frequent attacks of severe anginal pain since the time of the coronary occlusion. Two patients had suffered from the anginal syndrome for one and one-half and for six years respectively before the attack of coronary occlusion and for the same lengths of time had experienced practically constant pain in both shoulders. In both patients the pain in the shoulder had been more severe since the time of myocardial infarction.

The direction of radiation of the pain of coronary thrombosis appeared to be a factor of considerable importance in determining which shoulder was to be affected later. Periarthritis of the shoulder more commonly involves the right shoulder than the left¹. In contrast to this, the persistent pain which develops with or after coronary thrombosis affects the left shoulder much more commonly than the right, and the frequency with which the left shoulder is involved corresponds approximately with the incidence of radiation of the pain of coronary occlusion to the left shoulder and arm. Of 8 patients in whom the pain of coronary occlusion radiated only to the left shoulder and arm, the persistent pain involved the left shoulder in 6 and both shoulders in 2. In the single patient in whom the pain of the acute attack radiated only to the right shoulder and arm, persistent pain subsequently developed in both shoulders. The pain of coronary occlusion radiated to both shoulders in 3 patients. In 2 of these the right shoulder subsequently became persistently painful, while the other patient had had practically constant pain in both shoulders, as well as frequent attacks of angina pectoris for six years before the occurrence of coronary thrombosis. In 5 patients the pain of coronary occlusion did not radiate beyond the thorax, in 3 of these the left shoulder subsequently became painful, while in the other 2 both shoulders were involved. Among the entire 17 patients, the left shoulder alone was the site of persistent pain in 9, the right shoulder alone in 2 and both shoulders in 6.

The site of the myocardial infarct did not appear to be of importance with relation to the localization of the persistent pain in the shoulder.

In approximately two thirds of the patients, examination of the involved shoulder revealed local tenderness either about the joint or over the lateral aspect of the upper part of the arm and moderate or marked limitation of movement, especially of abduction and external rotation. In 5 patients, however, the range of motion was normal in all directions and no local tenderness could be elicited. Roentgen

1 Dickson, J. A., and Crosby, E. H. Periarthritis of the Shoulder. An Analysis of Two Hundred Cases, *J. A. M. A.* 99:2252-2257 (Dec. 31) 1932.

examination was made of the affected shoulders of several patients, but in only 1 patient were calcific deposits found in the region of the subdeltoid bursa

It is of interest that in 5 patients symptoms and local changes similar to those of rheumatoid arthritis appeared in other joints either at the same time as the development of the pain in the shoulder or shortly thereafter. One other patient had had pain in the shoulders and rheumatoid arthritis involving the fingers, elbows and back in association with angina pectoris for six years before the occurrence of coronary occlusion.

The known duration of the pain in the shoulder following myocardial infarction varied from less than three months to more than two years. In several instances the pain was still present at the time the patient was last heard from, so that no statement can be made concerning the maximum duration of symptoms. For the most part the pain seemed to pursue a self-limited course. In several patients the symptoms were not sufficiently severe to require special treatment. In the more severe disturbances, however, treatment consisted of the local application of heat by baking and diathermy and the oral administration of analgesics, but it usually was not possible to be sure that these measures shortened the duration of the disability.

The clinical course of the pain in the shoulder is exemplified in the following case report.

REPORT OF A CASE

A white man 57 years of age was seized with agonizing substernal pain while returning to his home from Florida by train. The pain radiated to both shoulders and down the inner aspects of both arms to the wrists. Two hypodermic injections of morphine sulfate gave only partial relief, and the pain persisted, but with gradually diminishing intensity, for twelve hours. The patient was admitted to the hospital twenty-four hours after the onset of the pain. At that time the temperature was 100.2 F, and the leukocyte count was 16,500 per cubic millimeter. The erythrocyte sedimentation rate was moderately elevated above the normal, and an electrocardiogram gave evidence of anterior myocardial infarction.

There was no recurrence of the substernal pain after the initial attack, and for three weeks the clinical course was entirely uneventful. The leukocyte count returned to normal on the seventh day, and the temperature did not rise above normal after the twelfth day. The erythrocyte sedimentation rate attained its maximum at the end of two weeks and then gradually became slower, but it did not reach a normal value until the end of the third month. Three weeks after admission to the hospital the patient began to complain of persistent pain in the right shoulder, at first mild and aching but gradually increasing in severity. Examination revealed an increasing degree of limitation of movement of the shoulder and tenderness over the lateral aspect of the upper part of the arm. Roentgenograms of the joint showed no pathologic changes. Diathermy and baking gave only partial and temporary relief from the pain. After three months the discomfort began to subside gradually, and by the end of the fourth month

it had disappeared entirely Two months later, however, stiffness, pain on motion and tenderness developed in the hands and feet, and a diagnosis of rheumatoid arthritis was made General measures of treatment were instituted, and all symptoms in the joints subsided after another two months

COMMENT

The occurrence of persistent pain in the shoulder region as a sequel to myocardial infarction has been commented on by only a few observers Howard,² Boas and Levy³ and Leech⁴ reported cases in which the clinical picture of the involved shoulder resembled that of peri-arthritis Edeiken and Wolferth⁵ also reported a series of cases, but their cases differed somewhat from those of the other observers inasmuch as the pain was not aggravated by ordinary movements of the arm and there was no local tenderness on pressure Cases of both kinds are included in the present report It is of interest that Edeiken and Wolferth estimated the incidence of the symptoms in the shoulder as in excess of 10 per cent among survivors of myocardial infarction In the present series of cases of myocardial infarction the incidence of pain in the shoulder amounted to 12 per cent, but in approximately two thirds of this number the characteristic features of peri-arthritis of the shoulder were present It may well be that the difference between the cases in which the condition resembled peri-arthritis and those in which there was no local tenderness or limitation of motion is one of degree only

The mechanism by which the pain is produced is not known Edeiken and Wolferth suggested an analogy to the causalgia which may follow obliteration of a peripheral artery Boas and Levy suggested two possibilities (1) that radiation of the anginal pain to a shoulder which was already the site of slight pain might, by summation, induce the painful discomfort or (2) that afferent pain impulses from the heart might lead to sensitization of the neurons whose fibers go to make up the brachial plexus They expressed the opinion that the latter of these two possibilities is a more probable explanation than the former It seems to us that there is still another possible mechanism, namely, that the symptoms develop as a result of relative disuse of the shoulder and abnormal tension of the muscles of the shoulder girdle During the

2 Howard, T Cardiac Pain and Peri-Arthritis of the Shoulder, *M J & Rec* **131** 364-365 (April 2) 1930

3 Boas, E P, and Levy, H Extracardiac Determinants of Site and Radiation of Pain in Angina Pectoris with Special Reference to Shoulder Pain, *Am Heart J* **14** 540-554 (Nov) 1937

4 Leech, C B Painful Shoulder in Association with Coronary Artery Disease, *Rhode Island M J* **21** 104-106 (July) 1938

5 Edeiken, J, and Wolferth, C C Persistent Pain in Shoulder Region Following Myocardial Infarction, *Am J M Sc* **191** 201-210 (Feb) 1936

period of strict rest in bed and the subsequent limitation of activity which are enforced on the patient who has had acute coronary thrombosis, the shoulder is used much less than normally. In addition, after the severe pain of coronary occlusion certain patients for a long time may unconsciously keep the muscles of the shoulder girdle on one or both sides in a state of abnormal tension as a protecting mechanism against the possible recurrence of pain. Tension of this kind might be expected to be greater on the side to which the pain of the coronary seizures radiated, and this theory would help to explain the relation between the direction of radiation of the cardiac pain and the site of the subsequent persistent symptoms in the shoulder. Once the pain has appeared in the shoulder, continued tensing of the muscles would be natural, and this tension in turn would explain the prolonged duration of the symptoms in so many patients. As matters stand at present, however, there is not sufficient evidence to enable one to state which of the above mechanisms is actually responsible for the development of the persistent pain.

There are certain practical reasons why this sequel to myocardial infarction is deserving of emphasis. Many patients when the persistent pain develops in the shoulder first interpret the symptoms as having resulted from some further injury to the heart. The physician is therefore consulted in alarm, and it obviously is of great importance that he be able to interpret the pain correctly. Furthermore, when one is consulted by a patient because of persistent pain in one or both shoulders, the possibility should be borne in mind that the trouble may have followed unrecognized coronary thrombosis. A careful cardiovascular history, therefore, should be taken, and this should include detailed questioning about recent attacks of "indigestion" or "gas." If the history is at all suggestive or if physical examination reveals abnormal cardiovascular findings, an electrocardiogram should be made. The tracing under such circumstances may show changes characteristic of myocardial infarction.

SUMMARY

The development of persistent pain in one or both shoulders is a relatively common sequel to myocardial infarction. The severity of the condition ranges from the clinical picture of typical periarthritides with intense pain and great limitation of motion to one of mild aching pain with a sensation of weakness but without loss of function. The left shoulder is affected more commonly than the right, and the symptoms persist for several weeks or months. In a few patients, changes similar to those of rheumatoid arthritis develop in other joints either simultaneously with or subsequent to the appearance of the symptoms in the shoulder.

The present report is based on 17 cases of persistent pain in the shoulder region encountered in a series of 133 consecutive cases of myocardial infarction. In 15 of these the pain dated from the attack of coronary occlusion or developed subsequent to the attack. In the other 2 the patients had suffered from angina pectoris and practically constant pain in both shoulders for a long time before the acute coronary attack. In both of them the pain in the shoulder increased in severity after the occurrence of myocardial infarction. In 6 of the 17 cases symptoms of rheumatoid arthritis involving other joints developed either simultaneously with or subsequent to the appearance of the symptoms in the shoulder.

The cause of the persistent pain in the shoulder region is unknown. The mechanisms which have been suggested as possible explanations in the past have been reviewed, and an additional hypothesis is proposed.

The practical significance of this sequel to myocardial infarction is pointed out.

INTERAURICULAR SEPTAL DEFECT

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In February 1938 there were 2 patients in the Lancaster General Hospital at the same time, both of whom showed large interatrial septal defects at necropsy. The purpose of this paper is to present the 2 cases and to review the literature since 1934, at which time Roesler made an extensive clinical study and a complete review of the literature on this subject. He collected 62 cases, including a case of his own.

REPORT OF CASES

CASE 1—A 76 year old white man, a locomotive engineer, was admitted to the hospital on Feb 17, 1938, complaining of headache, poor vision and a heavy feeling over the front of the chest.

He had had a sore throat many times as a child, scarlet fever, "lung fever" (at age of 10 years) and pneumonia (in 1935). At the age of 18 years he had a "bad heart" and was in bed for over a year. At 21 he went west and worked for twenty years as a locomotive engineer and as an operator of steam shovels. For the next fourteen years he was a postal clerk. During all this time he had no cardiac or other complaints.

About midnight on January 10 he was awakened in a terrible fright, he was short of breath and could not feel his pulse. This lasted about five minutes, after which he felt much better. His usual weight, 140 pounds (63.5 Kg), had fallen to 110 pounds (49.9 Kg) during the past year. He had had a nonproductive cough, edema of the ankles and increasing dyspnea for two weeks prior to admission.

On physical examination moderate clubbing of the fingers and considerable dyspnea were noted. There was marked scoliosis to the left in the upper part of the thoracic region, and the ribs on the right of the sternum protruded markedly. Marked cervical venous pulsations were noted. There was a diffuse and strong thrust at the cardiac apex. No thrills were felt. The heart was markedly enlarged to the left, and the point of maximal intensity was felt in the anterior axillary line. The apex was beyond the anterior axillary line on percussion. The rhythm was irregular, the rate was 80. A loud systolic murmur was heard all over the precordium but was heard best at the apex and was transmitted to the axilla. There was marked peripheral sclerosis. The blood pressure was 144 systolic and 64 diastolic. The liver was palpable 3 cm below the costal margin.

The value for hemoglobin was 58 per cent. There were 3,560,000 red cells and 5,000 white cells per cubic millimeter of blood. There was a faint trace of albumin in the urine. The Wassermann reaction of the blood was negative.

An electrocardiogram taken February 18 showed a slurred and low voltage QRS complex in all leads. The rhythm was nodal, with a tendency to bigeminy.

The clinical impression was that of rheumatic cardiovascular disease with decompensation, mitral insufficiency and marked myocardial dilatation. The patient became rapidly more dyspneic and died on February 23.

Autopsy was performed by Dr Louisa E Keasbey The main interest centered about the heart and lungs The lungs were pushed back out of view by the greatly enlarged heart The pulmonary artery was greatly enlarged

The pericardium was opened and was seen to contain a slight excess of fluid The heart was enormously enlarged, measuring 22 cm in its transverse diameter (the chest measured 31 cm) The heart weighed 860 Gm As viewed in situ there was marked rotation, so that the left ventricle was not apparent to inspection In situ there was observed a very large defect in the interauricular septum It measured 4.5 cm in length, it was oval, with somewhat cordlike edges, resembling a greatly enlarged foramen ovale which was devoid of any valvelike flap of tissue The right side of the heart was enormously enlarged, dilatation having great preponderance over hypertrophy The right auricle measured 12.5 cm in

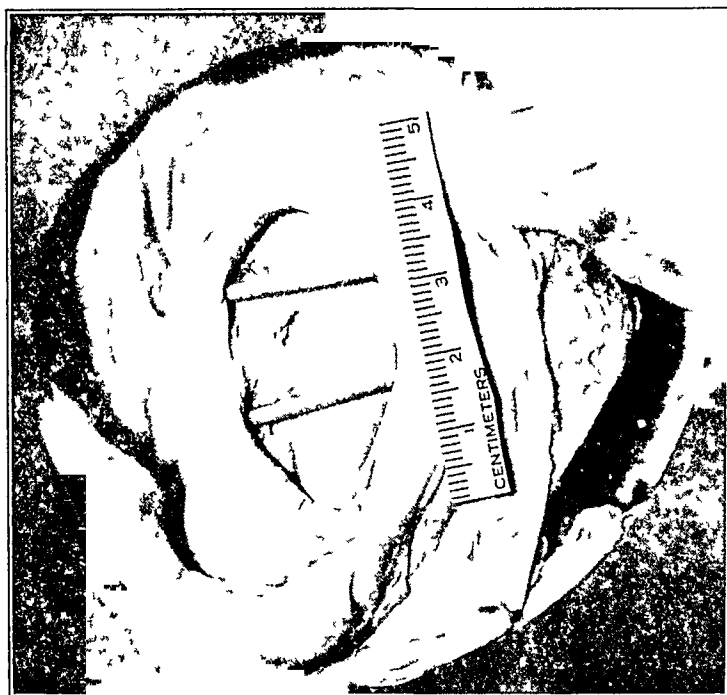


Fig 1—Defect in the interauricular septum

diameter and the tricuspid valve 14.5 cm in circumference The right ventricle was greatly dilated, with a maximum thickness of 1 cm The pulmonary artery was exceedingly enlarged, measuring 10 cm in circumference at the pulmonary valve and 9 cm at the point of bifurcation The inferior vena cava was greatly dilated and measured 7 cm in circumference at the entrance into the heart The left ventricle was on the posterior surface of the heart and did not appear to participate in the enlargement The wall of the left ventricle was 1.5 cm thick The aortic valve was 6 cm in circumference The mitral valve was 11 cm in circumference All surfaces of the heart were soft and pliable and were free of any evidences of endocarditis The coronary arteries showed slight sclerotic changes and were rather large, the main vessel being 1 to 1.5 cm in circumference The aorta showed evidence of atheromatous plaques, and moderate arteriosclerosis was present in the smaller vessels

The liver showed slight evidence of congestion of the nutmeg type It was not greatly enlarged

The kidneys were markedly congested, and arteriosclerosis was noted. The cortices were congested and swollen.

The anatomic diagnoses were interauricular septal defect and chronic passive congestion.

CASE 2—A 47 year old white man was admitted to the Lancaster General Hospital on Feb 4, 1938, complaining of weakness and shortness of breath.

He had suffered from typhoid fever in boyhood. A previous attack of cardiac decompensation had occurred three years prior to his admission to the hospital. There had been a "nervous breakdown" at the age of 18 years, following heavy drinking. There was no history of rheumatic fever.

His present illness had begun on January 15, after an alcoholic debauch. He had soon become weak and short of breath, and a cough, productive of a rather profuse greenish material, had developed.

The patient was well developed, showing slight dyspnea at rest. Fine rales were heard at the bases of both lungs, and there was marked dulness at the base of the right lung. There were no thrills. The heart was markedly enlarged on percussion, the left border being 14 cm from the midsternal line in the fifth inter-space. The sounds were very weak and distant, the rhythm was regular. A short systolic murmur was heard at the mitral area but was fleeting. The pulmonic second sound was greater than the aortic. The blood pressure was 100 systolic and 84 diastolic. The pulse rate was 90. The liver was very tender and extended almost to the umbilicus. There were marked edema of the extremities and slight clubbing of the fingers.

The value for hemoglobin was 82 per cent. There were 4,410,000 red cells and 8,000 white cells per cubic millimeter of blood. The Wassermann reaction of the blood was negative.

An electrocardiogram taken February 5 showed a 2:1 auricular flutter. Lead I showed a flat T wave, and there was low amplitude of the QRS complex in leads II and III. On February 17 the electrocardiogram showed a definite Q wave in lead III. On March 7 the electrocardiogram showed that auricular flutter had continued, uninfluenced by light quinidine therapy.

Fluoroscopic examination on February 5 showed tremendous cardiac hypertrophy and dilatation. The apex of the left ventricle was in the anterior axillary line. The right border was halfway to the right axillary line. Both sides of the diaphragm were almost completely obscured by the cardiac enlargement. The lung fields were very cloudy because of passive congestion. The aorta was slightly widened.

During his first three weeks in the hospital the patient appeared to improve, although a septic temperature and a totally irregular rhythm continued. However, he never regained full compensation. A second fluoroscopic examination, done on March 7, showed a large amount of fluid, filling at least two thirds of the right side of the thorax. The heart was tremendously enlarged, the amplitude of the pulsations was small. The apex of the heart was almost at the left costal margin. In the right anterior oblique position the posterior portion of the mediastinum was obscured by fluid. The aortic shadow was widened, hazy and difficult to visualize. In the left anterior oblique position there was extreme cardiac dilatation, the amplitude was very small. Thoracenteses on the right were performed on March 3, 17 and 22.

The clinical impression was that of myocardial hypertrophy and decompensation of unknown cause, with cirrhosis of the liver.

Autopsy was performed by Dr Louisa E Keasbey There was no fluid in the left side of the chest, but 1,000 cc of amber fluid was present on the right The right lung was edematous, weighing 730 Gm , the left weighed only 470 Gm

The pericardial cavity was opened, and a slight excess of pericardial fluid was noted The heart was greatly enlarged The transverse diameter in situ was 20 cm , the diameter of the chest was 30 cm The heart weighed 585 Gm There were two milk spots on the anterior surface The enlargement was greater on the right side, with a hypertrophied and dilated right ventricle and right auricle When the heart was opened a patent interatrial septum was seen The long diameter measured 4.5 cm This was partially occluded by a flap which acted in a valvelike fashion With the valve closed, one third of the communication remained patulous The diameters of the valves were as follows tricuspid, 1.1 cm , pulmonary, 0.85 cm, and mitral, 1.05 cm The diameter of the pulmonary artery at the hilus of the lung was 2.5 cm Grossly the valves appeared in good con-



Fig 2—Patent interatrial septum

dition The myocardium appeared somewhat degenerated and was soft and flabby The aorta was slightly calcified There were no mural thrombi The coronary vessels were of good size and slightly sclerotic

The spleen was enlarged, weighing 215 Gm It was pale and somewhat fibrotic The kidneys were markedly enlarged and were pale The liver was greatly enlarged, weighing 2,520 Gm It had a typical nutmeg appearance The gallbladder contained a small amount of green bile The bile ducts were patent

The pathologic diagnoses were patent interatrial septum, congestive heart failure with cardiac hypertrophy and dilatation, hydrothorax on the right, and early cirrhosis of the liver

All cases of interatrial septal defect which I could find in the literature since 1934 were reviewed, and a few of the results are presented (see table) Cases of slight patency of the foramen ovale were not included, since this is the commonest of all congenital cardiac defects, the incidence, according to Patten, being approximately 25 per cent

An attempt was made to include only those cases in which there existed a defect of about 1 cm or larger, but since the exact measurements were not always reported a few cases were also included in which were observed the following typical pathologic features (1) a widely patent foramen ovale, (2) marked hypertrophy and dilatation of the right auricle and ventricle, (3) relative enlargement of the pulmonary artery and its branches, and (4) relative smallness of the left ventricle and the aorta

Data in Twenty-Two Cases from the Literature

Author	Date	Patient's		Size of Aorta	Size of Pulmonary Artery	Description of Defect
		Age	Sex			
1 McGinn and White	1933	56	M		10.5 cm	2.4 by 1.5 cm
2 Yater, Barrier and McNabb	1934	57	F	Small	Very large	
3 Mitchell and Bauer	1934	40	M	5 cm	8.5 cm	1 by 3.5 cm
4 Joules	1934	37	F	Little finger	Aneurysm	Ostium secundum
5 Cesari	1935	30	F	1.6 cm	2.5 cm	2 by 1.6 cm
6 Gibson and Roos	1935	12	M	Hypoplastic	Very large	4 by 3 cm
7 Gibson and Roos	1935	25	M			4 cm
8 Sailer	1936	67	M	Small	Large	Ostium primum, 3 cm
9 McLeod	1936	33	F		Conus very large	2 by 1.1 cm
10 Cossio and Berconsky	1936	25	M			Large
11 Lutembacher	1936	61		2.5 cm	6.5 cm	Wide open
12 Lutembacher	1936	22	F	2.5 cm	4 cm	
13 Arana and Aguirre	1936	11	M	4.7	6.5 cm	1.5 by 1.4
14 Tarnover and Woodruff	1936	77	M	2/3 size of pulmonary artery	10.5 cm	4 cm
15 Cossio and Arana	1937		M	1.8 cm	3.0 cm	4.5 cm
16 Cossio and Arana	1937	53	M			2.1 by 2.3 cm
17 Cossio and Arana	1937	13	F	4.5 cm	6.5 cm	1.4 by 0.4 cm
18 Kutumbiah and Rao	1937	20	M	5.7 cm	10.5 cm	4 by 3 cm
19 Taussig, Harvey and Follis	1938	47	M	4.5 cm	9 cm	3 cm
20 Taussig, Harvey and Follis	1938	8¾	M	5.8 cm	6.4 cm	2 cm
21 Taussig, Harvey and Follis	1938	47	F	6.5	2 times size of aorta	5 cm
22 Taussig, Harvey and Follis	1938	9½	F	3.5 cm	6.5 cm	3 cm

ETIOLOGY

Most persons agree that the characteristic pathologic changes in the heart are consequent on the interatrial septal defect and consider this the primary lesion. The right side of the heart is so disproportionately dilated and hypertrophied because the blood is shunted from the left to the right atrium, thus depriving the left side of the heart of its usual load.

Lutembacher claimed that mitral stenosis in these cases is of congenital origin. By producing an increased pressure in the left auricle, the stenosis would ultimately cause a shunt of blood from the left to the right auricle through the patent foramen, which would, therefore, never

be able to close. There are many serious objections to this theory, the best being that in a fair percentage of cases of rather marked interatrial septal defect the condition is unaccompanied with mitral stenosis. Both cases presented here illustrate this point.

A congenitally hypoplastic aorta would also produce an increased pressure in the left side of the heart and have an effect similar to that of mitral stenosis. This should theoretically keep the foramen ovale open by a left to right shunt. However, in these 2 cases the aorta is not truly hypoplastic but only relatively smaller than the pulmonary artery.

PATHOLOGIC PICTURE

Originally the atrium is a single cavity. A septum grows down from the superior portion of this cavity to divide it into a right and a left auricle. This septum, known as the primary septum, meets a much smaller septum, known as the endocardial cushions, which has grown up from the inferior portion of the single atrium. When these two septums meet, the primary communication between the auricles, the ostium primum, is obliterated. The communication between the atria is reestablished when an opening is formed in the primary septum, known as the foramen ovale, or ostium secundum. A little later in fetal development another septum, known as the septum secundum, grows down to the right of the primary septum and after birth eventually fuses with the primary septum, thereby obliterating the foramen ovale. Any failure in the union of the primary septum and the inferior portion of the auricle causes a persistent ostium primum. Any failure of union between the primary septum and the septum growing down to the right of it causes a persistent ostium secundum or a patent foramen ovale.

The typical pathologic changes are well exemplified in these 2 cases. I have classified both as cases of typical persistent ostium secundum.

The right auricle and ventricle in both cases were markedly hypertrophied and dilated, dilatation exceeding hypertrophy. In both the left side of the heart was relatively small. There were also marked dilatation and hypertrophy of the pulmonary artery, causing it to exceed the size of the aorta in both cases, although the aorta was only relatively smaller and could not be considered truly hypoplastic.

There was no pathologic evidence of any chronic valvular defects in the heart in either case. This is rather unusual, since Roesler found that in three fourths of his series of 62 cases the condition was complicated by chronic valvular defects. In 15 of the 22 cases which I reviewed there were complicating valvular lesions. In 11 of these the lesion was mitral stenosis.

CLINICAL PICTURE

Approximately 61 per cent of all interatrial septal defects are found in females. Both patients described here were men.

Cyanosis is present only in the very late stages of this disease, when the increased pressure in the right atrium causes a right to left shunt. One third of the blood must be shunted before cyanosis is produced. The condition has therefore been classified by Abbott as *cyanose tardive*.

In contrast to the picture of many other congenital cardiac diseases, clubbing is rarely found and, when present, is usually slight in cases of uncomplicated interatrial defects. Very slight clubbing was found in only 3 of the cases reviewed. Both patients described here showed clubbing.

Thrills are an inconstant finding, being recorded in only 8 of the 22 cases reviewed. In 7 the thrill was systolic, in 1 it was systolic and diastolic. Murmurs are variable. The commonest finding is a systolic murmur in the third left interspace, rather closely simulating that associated with *maladie de Roger* except that it is usually slightly higher and not so intense. As would be expected with any condition in which such a large burden is placed on the right side of the heart, the pulmonic second sound is usually greater than the aortic, although this finding is of little diagnostic value in those cases complicated by mitral stenosis.

The heart is enlarged both to the right and to the left of the sternum, the enlargement to the left being caused by hypertrophy and dilatation of the right auricle and ventricle plus counterclockwise rotation of the heart.

Since the pathologic process is present from birth, most patients show a deformity of the left side of the chest.

Pulsation of the veins of the liver and of the neck is common, particularly when the condition is complicated by a pathologic condition of the tricuspid valve.

The antemortem diagnosis of this condition is rarely made, but it can be greatly facilitated by roentgen and fluoroscopic examinations, which reveal an enlarged, globular heart (most of the enlargement being in the right auricle and right ventricle), very wide hilar shadows (often pulsating and mistaken for tuberculosis or tumor), a greatly enlarged pulmonary arch and a very small aortic knob. The contour of the left side of the heart is formed almost entirely by the right ventricle. Counterclockwise rotation of the heart takes place. Contrary to the opinion of Lutembacher, the typical "*coeur en sabot*" configuration is not seen.

The electrocardiogram usually shows right axis deviation and high P waves. Auricular fibrillation is common.

PROGNOSIS

The prognosis of this condition is not necessarily bad, as is well substantiated by the ages of these 2 patients. The average age of

the patients in Roesler's series was 36 years. The average age of the patients in the 22 cases reviewed since 1934 was 34.8 years. If the 2 patients described here are included the average age is raised to 37 years.

Since three fourths of all interatrial septal defects are complicated by chronic valvular lesions, the prognosis of the defect alone is rather difficult to ascertain. However, Roesler found that the presence of a chronic valvular lesion did not materially affect the prognosis. The oldest patient described in the literature since 1934 was the patient of Tarnover and Woodruff, who lived to be 77. Our first patient was 76.

COMPLICATIONS

Although a superimposed rheumatic infection is one of the most frequent complications, no pathologic evidence of such an infection was found in the heart in either case. In 68 per cent of the 22 cases reviewed there were chronic valvular lesions. In 50 per cent there was mitral stenosis.

Roesler stated that chronic pericardial disease is practically absent. He was able to find only 1 case in his review, and the patient had chronic extensive pulmonary tuberculosis. There have been 3 cases reported since Roesler's review in which chronic pericarditis was present as a complication.

There have been no cases reported in which subacute bacterial endocarditis was present, although this complication is frequently found in association with other congenital malformations of the heart.

Auricular fibrillation is rather rare in association with other congenital malformations of the heart, but it is very common with interatrial septal defect. In 7 of the 22 cases which we reviewed there was auricular fibrillation, in 3 there was auriculoventricular block, and in 2 of the latter the Stokes-Adams syndrome was observed.

Pulmonary infections and emboli occur very often and, together with cardiac decompensation, usually cause the death of the patient.

SUMMARY AND CONCLUSIONS

Two cases of uncomplicated interatrial septal defect are presented. The respective ages of the patients were 76 and 47.

A review of the literature since 1934 has revealed 22 cases of interatrial septal defect. Roesler's review in 1934 included 62 cases. This brings the total number of cases reported to 86, including the 2 reported here.

The characteristic pathologic features in addition to the septal defect are marked hypertrophy and dilatation of the right auricle, the right ventricle and the pulmonary artery. The left auricle, the left ventricle and the aorta are all relatively small.

The only way to be sure of a correct diagnosis is by roentgen or fluoroscopic examination. There are four characteristic features: increased hilar shadows, great enlargement of the right side of the heart, a small aortic knob and a very large pulmonary conus.

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RELATIVE SIGNIFICANCE OF CONCENTRATION OF INORGANIC SULFATE IN THE SERUM AND OF ITS RENAL CLEARANCE

WITH SPECIAL REFERENCE TO DIFFUSE ARTERIOLAR
DISEASE WITH HYPERTENSION

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The accumulation of inorganic sulfate in human serum above normal limits in advanced stages of renal disease was first observed by Denis¹ in 1921. Subsequent work by various groups of investigators (Denis and Hobson,² Loeb and Benedict,³ Cope,⁴ Hayman and Johnston⁵) substantiated these observations. Wakefield, Power and Keith⁶ pointed out that sulfate, the concentration of which normally is not in excess of 5.5 mg⁷ per hundred cubic centimeters of serum, in an appreciable number of cases actually is the first substance to accumulate in the blood of patients with early renal insufficiency. Macy,⁸ amplifying the scope of the problem, investigated the clearance of inorganic sulfate. He found a

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8 Macy, J. W. Significance of the Inorganic Sulphate Clearance in Renal Disease, *Arch Int Med* **54** 389-404 (Sept) 1934

certain number of patients in whom renal damage could be expected to exist whose clearance of inorganic sulfate was less than 20 cc per minute (which he considered the lower limit of normal), whereas with none of the other tests of renal function studied were the results considered indicative of diminished capacities of the kidney. Curiously enough, a few instances were observed in which retention of inorganic sulfate in the serum had taken place without its rate of excretion as measured by the sulfate clearance test having fallen below normal limits.

Apparent inconsistencies of this nature continue to be observed from time to time. Since not enough fundamental facts about the mechanism of excretion of the sulfate ion were available to explain the anomalous situation, one of us (Goudsmit), in collaboration with Power and Bollman,⁹ made a study of various factors which might influence its rate of excretion in dogs. Among other features, their findings revealed that the sulfate clearance was greatly increased by relatively small increases in the level of sulfate in the plasma, produced by intravenous injection of sodium sulfate. Thus, raising the normal concentration of plasma sulfate 100 per cent brought about an increase of clearance of approximately 500 per cent. This is in agreement with the earlier observations of White and Monaghan,¹⁰ who established this relation qualitatively in experiments on the dog.

In man, sulfate clearance similarly undergoes an increase after the concentration of sulfate in the plasma has been raised by intravenous administration of sodium sulfate (Hayman and Johnston,⁵ Power, Goudsmit and Keith¹¹). This increase is relatively smaller than that observed in the dog. Cope, on the other hand, was unable to observe an increase of the clearance of inorganic sulfate after its concentration in the plasma had been nearly doubled by oral administration of sodium sulfate. However, the value for normal clearance of endogenous sulfate in man reported by this author is considerably greater than that usually found in publications of other workers in the field.

METHODS OF STUDY

General Outline of Investigation—The question thus arises whether the increased concentration of sulfate in the plasma in patients with renal disease may not in itself be the cause of the increased sulfate clearance seen occasionally under these circumstances. In an attempt to find an answer, we set out to study a group of patients with values for inorganic

9 Goudsmit, A., Jr., Power, M. H., and Bollman, J. L. The Excretion of Sulfates by the Dog, *Am J Physiol* **125** 506-520 (March) 1939.

10 White, H. L., and Monaghan, B. A Comparison of the Clearances of Various Urinary Constituents, *Am J Physiol* **104** 412-422 (May) 1933.

11 Power, M. H., Goudsmit, A., Jr., and Keith, N. M. Sulfate and Sucrose Clearances in Normal Men, *J Biol Chem* **128** lxxx-lxxx (June) 1939.

sulfate in excess of the upper limits of normal, or 5 mg per hundred cubic centimeters of serum (group A), and to compare the sulfate clearances with those observed in a control group (B) of patients in whose cases values for serum sulfate of less than 5 mg per hundred cubic centimeters were observed. In order to have more complete data in regard to renal functional changes in both these groups, values for urea clearance were obtained at the same time as those for sulfate clearance. The ratio of sulfate clearance to urea clearance was then calculated for each individual clearance period.

The selection of the cases was accomplished as follows. From the records of patients for whom sulfate clearance had been determined between Jan 1 and Oct 8, 1938, inclusive, all those with (1) values for inorganic sulfate in the serum exceeding 5 mg per hundred cubic centimeters and (2) a rate of flow of urine of at least 2 cc per minute were chosen for group A (24 patients). During this period, 194 determinations of sulfate clearance showing a rate of urinary flow of at least 2 cc per minute were performed on patients for whom a value for inorganic sulfate of less than 50 mg per hundred cubic centimeters of serum had been recorded. From their much larger number 26 were taken to form group B. In the case of each, a test usually had been made on the same day as one of the observations in group A.

When we checked back on the cases of the patients represented, they appeared to include 38 cases of diffuse arteriolar disease with hypertension and 11 cases of miscellaneous renal disease. In 1 case there was neither hypertension nor evidence of renal disease. The essential data collected are summarized in table 1.

Detailed Renal Functional Analysis—For the purpose of a closer analysis, renal efficiency has been studied in each of the clinical groups. "Normal" function of the kidney was considered to exist (1) so long as the blood urea was maintained at a concentration not exceeding 46 mg per hundred cubic centimeters,¹² (2) so long as the urea clearance measured 50 cc per minute or more,¹³ (3) so long as the value for

12 Only very rarely did the concentration of urea in the blood exceed this figure in MacKay and MacKay's extensive series of "normals" (MacKay, E. M., and MacKay, L. L. The Concentration of Urea in the Blood of Normal Individuals, *J. Clin. Investigation* 4: 295-306 [June] 1927).

13 Usually 60 cc per minute is cited as the lower limit of the normal maximal blood urea clearance, and our nonconformance to this "accepted" figure is deliberate. At the Mayo Clinic we have not made it a practice to correlate urea clearance to body build, for example, surface area, and then express it as "per cent of normal." This probably is in part responsible for the fact that we are frequently confronted with values between 50 and 60 cc per minute without being able to detect renal or vascular disease in the patient investigated. An additional reason for our indulgence in this respect is the fact that the maximal urea clearance of one of us is definitely below 60 cc per minute.

TABLE 1—*Excretion of Sulfate and of Urea as an Index of Renal Function
A Comparative Analysis (Fifty Patients)*

Case No	Sex	Age	Serum Sulfate, Mg per 100 Cc	Sulfate Clearance, Cc / Min	Blood Urea, Mg per 100 Cc	Urea Clearance, Cc / Min	Urine Volume, in 1 Hr, Cc	Ratio of Sulfate Clearance to Urea Clearance	Diagnosis
19	M	51	14.6	11.3	148	10.8	142	1.05	Chronic nephritis of mixed type, multiple myelomas
5	M	56	12.0	21.8	120	15.5	250	1.41	Chronic glomerulonephritis (?) with mild secondary vascular disease and anemia
12	F	58	11.5	40.5	56	49.2	153	0.82	D A D * group 3*
20	F	33	9.9	13.6	110	12.4	210	1.10	Chronic glomerulonephritis with mild secondary vascular disease
1	M	52	8.1	12.1	98	15.1	307	0.80	Chronic glomerulonephritis with mild secondary vascular disease
24	M	43	6.8	55.9	76	56.6	250	0.99	D A D group 4, early congestive heart failure
26	F	62	6.8	13.0	36	46.1	245	0.28	D A D group 2
14	M	52	6.7	24.2	62	26.6	140	0.91	D A D group 2 with congestive heart failure
9	F	60	6.4	21.9	50	35.2	390	0.62	D A D group 3
32	M	32	6.3	23.2	52	20.5	126	1.13	D A D group 4
40	M	48	6.3	26.5	48	40.2	295	0.66	D A D group 3
38	M	40	6.1	22.3	36	55.8	568	0.40	D A D group 3
45	M	46	6.1	33.7	68	34.9	198	0.97	D A D group 4
42	M	52	6.0	78.0	34	75.0	300	1.04	D A D group 2, generalized arteriosclerosis, residual hemiplegia, "respiratory infection"
16	M	67	5.9	33.9	52	35.9	238	0.94	D A D group 3
36	M	67	5.8	18.4	40	33.5	222	0.55	D A D group 2, gout (?)
3	F	50	5.7	43.8	39	67.6	145	0.65	D A D group 2, considerable edema both lower extremities (neither cardiac nor nephritic)
29	M	59	5.6	49.0	20	69.6	245	0.70	D A D group 2, with general arteriosclerosis, recent cerebrovascular accident
34	M	36	5.6	27.0	58	28.5	126	0.95	Nephritis (?), diabetes mellitus,† grade 3, hyperlipemia, generalized arteriosclerosis
43	F	49	5.6	14.4	62	24.2	287	0.60	D A D group 3
22	F	48	5.6	21.7	42	34.5	347	0.63	D A D group 4
49	M	55	5.5	58.0	46	86.4	210	0.67	D A D group 2, with considerable arteriosclerosis
47	M	48	5.1	28.2	40	60.3	225	0.47	D A D group 4, with myocardial insufficiency
7	M	73	5.1	89.2	52	43.6	125	2.05	D A D group 2, with auricular fibrillation and myocardial failure
6	F	19	4.9	20.6	30	30.7	420	0.67	Chronic glomerulonephritis with mild secondary anemia
21	F	40	4.4	26.2	54	40.2	180	0.65	D A D group 1, obesity, congestive heart failure
11	M	57	4.4	14.5	22	48.9	275	0.30	D A D group 1
28	M	66	4.2	23.1	27	36.3	243	0.64	D A D group 2
35	F	58	4.2	14.2	24	20.1	124	0.71	D A D group 2 nephritis latent diabetes with diabetic retinitis
4	F	60	4.0	11.6	15	47.2	145	0.25	D A D group 2
2	M	56	3.9	26.6	38	51.5	318	0.52	D A D group 3
33	F	57	3.9	23.0	30	55.5	280	0.41	D A D group 3
41	M	29	3.9	37.6	38	90.4	430	0.42	Transient albuminuria
37	M	43	3.9	38.5	42	55.7	134	0.69	D A D group 1
23	F	18	3.8	20.0	16	47.7	660	0.42	Toxic (?) nephritis degenerative hepatitis
46	M	44	3.8	46.0	30	63.4	364	0.73	Essentially normal

TABLE 1—*Excretion of Sulfate and of Urea as an Index of Renal Function
A Comparative Analysis (Fifty Patients)—Continued*

Case No	Sex	Age	Serum Sulfate,		Sulfate Clearance,		Blood Urea,		Urea Clearance,		Urine Volume, in 1 Hr., Cc	Ratio of Sulfate Clearance to Urea Clearance	Diagnosis
			Mg per 100 Cc	Cc / Min	Mg per 100 Cc	Cc / Min	Mg per 100 Cc	Cc / Min	Mg per 100 Cc	Cc / Min			
8	M	52	3.7	16.2	33	20.4	150	0.79	D A D group 3				
39	F	52	3.7	28.0	36	50.1	282	0.56	Chronic unilateral pyelonephritis, chronic lymphatic leukemia				
13	M	53	3.6	32.0	26	58.8	320	0.51	Mild urinary tract infection previous nephrectomy, diabetes mellitus grade 3 4				
31	M	66	3.6	23.2	42	33.4	209	0.69	D A D group 2, generalized arteriosclerosis, previous transurethral prostatic resection				
27	M	48	3.6	24.4	28	55.8	200	0.44	D A D group 2				
50	F	70	3.6	28.1	26	22.8	145	1.23	D A D group 2, recent cerebral vascular accident				
18	F	40	3.4	13.5	24	17.2	230	0.79	D A D group 2				
25	F	58	3.2	70.0	30	62.7	800	1.12	D A D group 2, adenomatous goiter without hyperthyroidism				
48	F	51	3.1	32.0	18	51.2	355	0.63	D A D group 2				
44	F	20	3.1	14.1	24	27.2	240	0.52	Chronic glomerulonephritis (latent)				
10	M	35	2.9	48.9	32	83.3	506	0.59	D A D group 1				
15	F	63	2.8	38.4	30	33.9	336	1.13	D A D group 2 arteriosclerotic type, thrombosis of central retinal vein				
30	F	52	2.8	38.5	24	46.4	330	0.83	D A D group 2				
17	M	54	2.6	50.8	18	87.5	300	0.58	D A D group 1 diabetes mellitus grade 3				

* "D A D" stands for diffuse arteriolar disease with hypertension of groups 1, 2, 3 and 4, respectively, according to Keith and Wagener's classification. Group 4 corresponds to "malignant hypertension."

† Diabetes mellitus grade 2 denotes the stage in which a quantitative diabetic diet alone allows the adult patient to remain essentially nonglycosuric. Grade 3 indicates that the administration of 30 units of insulin or less per twenty four hours is necessary. All patients requiring more than 30 units of insulin per twenty four hours are classified as belonging to group 4.

serum sulfate did not exceed 5 mg per hundred cubic centimeters,¹⁴ or (4) so long as sulfate clearance amounted to a minimum of 25 cc per minute.¹⁵ An analysis of the frequency with which renal sufficiency or insufficiency was encountered is summarized in table 2.

All clearance studies were conducted in the manner described by Macy. The values for sulfate were determined according to the method of Power and Wakefield, those for urea, essentially according to the method of Van Slyke and Cullen.¹⁶

14 Described in the introductory paragraphs of this paper.

15 Macy considered 20 cc per minute the lower limit of normal sulfate clearance. In the present article the dividing line between "normal" and "pathologic" has been raised in accordance with our added clinical experience. It happens that in the complete series the number of patients with values for sulfate clearance of less than 25 cc per minute approximately equals the number of cases in which an increased value of sulfate in the serum was encountered.

16 Van Slyke, D. D., and Cullen, G. E. The Determination of Urea by the Urease Method, *J Biol Chem* **24** 117-122, 1916.

RESULTS

Clinical Correlation—A summary of the essential findings relating to the apparent ability of the kidneys of the patients studied to excrete urea and inorganic sulfate is presented in table 2. The group of patients with renal disease was too small and etiologically and clinically too heterogeneous for further analysis.

Of the 38 patients with hypertension, the majority had been hospitalized for closer evaluation of their condition, for the treatment of complications or for the management of nonrelated conditions. Of these, 24

TABLE 2—*Data Pertaining to Renal Function in a Group of Thirty-Eight Patients with Diffuse Arteriolar Disease with Hypertension and Eleven Patients with Renal Disease*

	Number of Patients with		
	Hypertension, Groups 1 and 2†	Hypertension, Groups 3 and 4†	Renal Disease
Urea concentration in blood			
46 mg per 100 cc and less	21	6	7
More than 46 mg per 100 cc	3	8	4
Impaired renal function,* percentage	13	57	36
Urea clearance			
50 cc per minute and more	10	5	3
Less than 50 cc per minute	14	9	8
Impaired renal function,* percentage	58	64	73
Inorganic sulfate concentration in serum			
5 mg per 100 cc and less	16	3	6
More than 5 mg per 100 cc	8	11	5
Impaired renal function,* percentage	33	79	45
Inorganic sulfate clearance			
25 cc per minute and more	14	7	4
Less than 25 cc per minute	10	7	7
Impaired renal function,* percentage	42	50	64
Total number of patients	24	14	11

* "Impaired renal function" refers to the percentage of instances in which impaired renal function was demonstrated by test immediately above in the table.

† The different groups of hypertension refer to the classification of Keith and Wagener.

were classified as having diffuse arteriolar disease with hypertension groups 1 and 2 (the less severe types according to Keith and his associates¹⁷), and 14 were classified as having diffuse arteriolar disease with hypertension groups 3 and 4 (groups having a serious prognosis). One patient, though similar in many respects to patients with the more serious types of hypertension, failed to show enough retinitis to be truly representative of group 3 and has been included as belonging to group 2.

17 Keith, N. M., Barker, N. W., and Kernohan, J. W. Histologic Studies of the Arterioles in Various Types of Hypertension, *Tr. A. Am. Physicians* **46**: 66-70, 1931. Keith, N. M., Wagener, H. P., and Barker, N. W. Some Different Types of Essential Hypertension: Their Course and Prognosis, *Am. J. M. Sc.* **197**: 332-343 (March) 1939.

Concentration of Sulfate in the Serum—The comparative analysis of the level of renal function associated with these groups of hypertension is especially interesting (table 2). No matter what criterion is used, it appears to be the rule that the excretory powers of the kidneys are diminished in patients with the severe degrees (groups 3 and 4) of diffuse arteriolar disease with hypertension (notable individual exceptions can be found in table 1), and apparently a most significant difference between the two groups is related to the concentration of sulfate in the serum. In the cases of 16 out of the 19 patients in whom a concentration of 5 mg or less per hundred cubic centimeters of serum was encountered, diffuse arteriolar disease with hypertension group 1 or 2 was diagnosed, and only 33 per cent of all patients with hypertension group 1 or 2 showed the presence of serum sulfate in increased amounts. Conversely, of all the patients who had diffuse arteriolar disease with hypertension groups 3 and 4, 79 per cent, or 4 of every 5, had a concentration of sulfate above 50 mg per hundred cubic centimeters of serum.

Sulfate Clearance—The incidence of normal and abnormal values for sulfate clearance is evident from a consideration of the last line but one (table 2), of the patients with diffuse arteriolar disease with hypertension groups 1 and 2, 42 per cent showed diminished sulfate clearance. However, in patients with diffuse arteriolar disease with hypertension groups 3 and 4, of whom approximately two and one-half times as great a percentage showed increased sulfate in the serum, there was hardly any higher incidence of diminished sulfate clearance. It is thus remarkable that the proportion of patients showing retention of sulfate (79 per cent) is considerably in excess of the proportion (50 per cent) showing diminished sulfate clearance. In other words, retention of sulfate in the blood serum may often be accompanied by "normal" clearance of sulfate.

Thus, the present series includes 12 cases in which normal clearance values for sulfate were found in the cases of patients with increased amounts of inorganic sulfate in the serum. This seemingly contradictory situation had been observed previously by Macy and was partly responsible for the present investigation. It was subjected to a closer analysis by comparing the ratio of sulfate clearance to urea clearance in our original two groups of cases, namely, persons with normal and persons with increased concentrations of sulfate in the serum. For the former group (those with normal concentration of sulfate in the serum) the ratio of sulfate clearance to urea clearance averaged 0.65, for the latter group (those with increased concentration of sulfate in the serum) this figure was 0.85. The difference between these clearance ratios in our two groups is significant, as is shown by the analysis of our figures.

summarized in table 3, and appears to be fundamentally related to all the seemingly contradictory data on sulfate excretion brought out by previous investigators as well as by the results of this study

Excretion of Urea—A survey of the various data pertaining to the excretion of urea in this same group of patients shows at once the similarity and the differences between the patterns of excretion of urea and of sulfate. The following facts may be noted: 1. In diffuse arteriolar disease with hypertension groups 1 and 2 (13 per cent) an increased concentration of blood urea was noted only infrequently. 2. In the presence of hypertension groups 3 and 4, more than half of the patients displayed an increased concentration of urea in the blood. 3. Only a small decrease of the percentage of those who had a urea clearance

TABLE 3—*Comparison of the Ratio of Sulfate Clearance to Urea Clearance in Subjects with an Increased Concentration of Inorganic Sulfate in the Serum with the Ratio for Subjects with Normal Concentrations of Inorganic Sulfate in the Serum*

	Number of Cases	Ratio of Sulfate Clearance to Urea Clearance	
		Mean	Standard Deviation
Subjects with increased serum sulfate	24	0.85	0.36
Subjects with normal serum sulfate	26	0.65	0.24
	Difference = 0.20		
	S. D. of difference = 0.09		
$T = \frac{0.20}{0.09} = 2.22$		$P = 0.03$	

T is used to test the significance of the difference between the means. P gives the probability of such a value of T occurring by chance (Fisher, R. A. *Statistical Methods for Research Workers*, ed. 4, Edinburgh and London, Oliver and Boyd, 1932).

within normal limits was noted when the patients suffering from diffuse arteriolar disease with hypertension groups 1 and 2 were compared with those with hypertension groups 3 and 4. This comparative analysis definitely establishes the fact that in the more severe degrees of hypertension, as contrasted with milder forms, there is a far greater probability that either urea or sulfate will be retained in the blood than that decreases in the renal clearances of these two substances will be detected. 4. Retention of urea in the presence of a normal urea clearance is a rare finding. In only 1 (case 24) of the 50 cases studied was the urea clearance within normal limits when an actual accumulation of urea in the blood above normal limits had taken place. This is to be contrasted with the frequency with which the analogous situation is encountered with respect to sulfate, as was elaborated on earlier in this paper. A graphic analysis of many features of urea and sulfate excretion based on the patients investigated in this study is to be found in charts 1 and 2.

COMMENT

General Considerations—If the state of renal excretory function as revealed by clearance tests prevailed for twenty-four hours a day, the results of those tests (for a given twenty-four hour level of excretion and assuming continuous production in the intermediary metabolism) should determine the amounts of any substance in the blood. Ingenious formulas have been devised to “translate” the work of excretion at

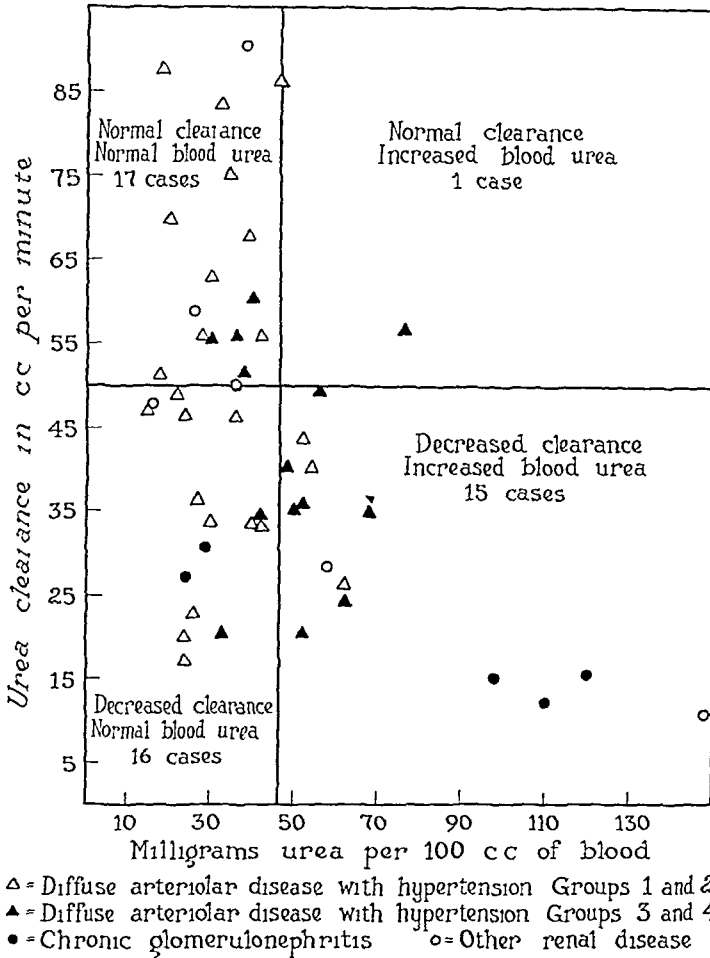


Chart 1—Pattern of excretion of urea in patients with diffuse arteriolar disease with hypertension and renal disease. The horizontal line divides the “normal” (above) from the “decreased” range of clearances (below). The vertical line divides “normal” (left) from “increased” values in the blood and serum (right). Similarity of the manner in which urea and sulfate are eliminated in the group of patients studied is indicated by the similar frequency of the individual observations in the right lower and left upper and lower quadrants of this chart and of chart 2. The salient difference involves the frequency of combination of “increased” blood (serum) concentration with “normal” clearances represented in right upper quadrant. Whereas only 1 instance is observed in excretion of urea it is encountered 12 times in the pattern of excretion of inorganic sulfate.

lower urine volumes into "standard" clearances, but this should not make one forget that at the usually prevailing relatively low (that is, as compared to those existing under conditions of "maximal clearance") rates of excretion of urine reabsorption takes place much more than is ordinarily observed in clearance studies. Thus, for urea, Chesley¹⁸ was able to show that below a critical lower level of urinary flow (0.35 cc per minute) urea clearance is directly proportional to urine volume

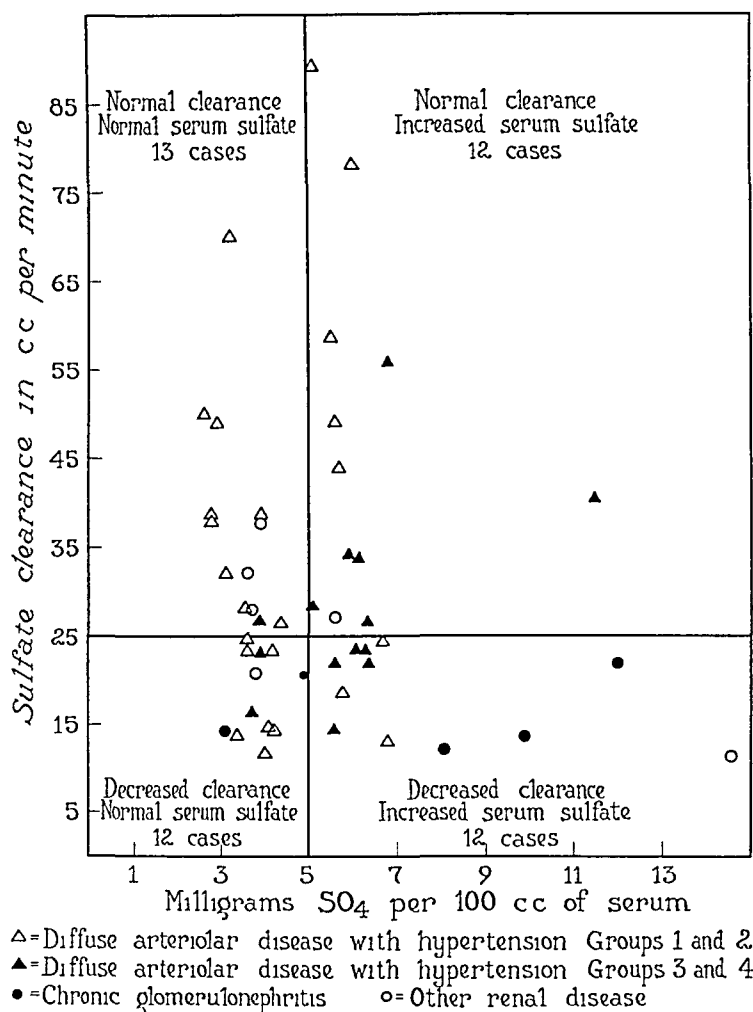


Chart 2—Pattern of excretion of inorganic sulfate in patients with diffuse arteriolar disease with hypertension and renal disease. Note the comment in the legend for chart 1.

The observations by Hayman and Johnston and by Macy point to a continuously decreasing rate of excretion of inorganic sulfates with diminishing flow of urine. Thus, for practical purposes a given "clearance" does not rigidly imply such and such a concentration in the blood, a fact which is well illustrated by the considerable statistical

¹⁸ Chesley, L. C. Urea Excretion at Low Urine Volumes. The Calculation of "Minimal" Urea Clearance, *J. Clin. Investigation* **17** 119-123 (March) 1938.

scattering in the well known figures of Van Slyke and his associates,¹⁹ who plotted blood urea against urea clearance

Serum Sulfate—These considerations make it understandable that the concentration of a given waste product in the blood may have a significance which would not appear from the analysis of its rate of excretion under optimal circumstances of removal. Inorganic sulfate apparently is one of these substances. In addition to the importance of its retention in the blood, noted by other authors, its accumulation in 4 of every 5 cases of diffuse arteriolar disease with hypertension groups 3 and 4 (which comprise those cases in which there is a hypertensive vascular type of retinitis), as has been reported earlier in this paper, is striking. It appears worthy of note that, whereas in the two other clinical groups studied (table 2) the value for urea clearance is most likely to be indicative of renal damage, the value for concentration of serum sulfate is most likely to point to the diminished renal function in the group with hypertensive vascular retinitis.

This peculiar correlation definitely indicates the intimate relation between renal damage sufficient to bring about actual retention of an end product of normal protein metabolism and hypertensive vascular disease severe enough to be associated with retinitis in human beings. The assumption that arteriolar changes, whether due to an imbalance of physiologic forces, such as vasospasm, or to actual pathologic changes, carry a great deal of responsibility for both renal and retinal disturbances appears rather obvious in the light of present knowledge of the pathologic physiology of this disease.

Sulfate Clearance—A review of the data submitted in table 1 indicates that "normal" and "decreased" values for sulfate clearance are equally distributed among the patients showing "normal" and "increased" concentrations of inorganic sulfate in the serum, practically one-half of the patients in each group having normal and one-half having diminished values for clearance of inorganic sulfate. This is clearly in contrast to the behavior of urea clearance in these two groups of patients, since the group with normal values for serum sulfate contained 58 per cent more patients with normal values for urea clearance than did the group with the values for serum sulfate above 50 mg per hundred cubic centimeters.

The more detailed comparative analysis submitted earlier in this paper shows that the value for sulfate clearance as compared to that for urea clearance increases as inorganic sulfate in the blood accumulates above the normal concentration. In its turn, the value for urea clearance

19 Van Slyke, D. D., McIntosh, J. F., Moller, E., Hannon, R. R., and Johnston, C. Studies of Urea Excretion. VI. Comparison of the Blood Urea Clearance with Certain Other Measures of Renal Function, *J. Clin. Investigation* 8: 357-374 (April) 1930.

does not maintain a constant ratio to the amount of "glomerular filtrate" as urea clearance becomes lower and lower with increased renal damage Chasis and Smith²⁰ showed that the ratio of urea clearance to inulin clearance increases as urea clearance diminishes and that it approaches unity in the presence of the severest degree of renal insufficiency This the authors stated to be due to the diminishing tubular reabsorption which goes hand in hand with the diminished concentrating power of the kidney This approximation of the clearances with increasing urinary dilution can be reproduced in healthy dogs by submitting them to forced diuresis through intravenous administration of a solution of sodium sulfate, sucrose or urea (Shannon²¹)

Presumably the mechanism of excretion of sulfate, like that of excretion of urea, consists in ultrafiltration by the glomeruli followed by partial reabsorption by the tubules, with this difference, that the fraction of sulfate reabsorbed is greater than that of urea, since the value for sulfate clearance for practically all healthy persons is lower than that for urea The potential capacity for reabsorption by the tubules of the healthy person, however, is much more limited for sulfate (Power, Goudsmit and Keith) than it is for urea²²

When the concentrating power of the kidney fails with advancing renal insufficiency, sulfate clearance as well as urea clearance tends to approach the level of inulin clearance Thus, Keith, Power and

20 Chasis, H, and Smith, H W The Excretion of Urea in Normal Man and in Subjects with Glomerulonephritis, *J Clin Investigation* **17** 347-358 (May) 1938

21 Shannon, J A Urea Excretion in the Normal Dog During Forced Diuresis, *Am J Physiol* **122** 782-787 (June) 1938

22 The latter mechanism namely, the "unlimited" reabsorption of urea by the tubules, curiously enough, can be arrived at by inference only the studies by T Addis and D R Drury (The Rate of Urea Excretion V The Effect of Changes in Blood Urea Concentration on the Rate of Urea Excretion, *J Biol Chem* **55** 105-111 [Feb] 1923) and by Drury (The Rate of Urea Excretion VI The Effect of Very High Blood Urea Concentrations on the Rate of Urea Excretion, *ibid* **55** 113-118 [Feb] 1923) do not include data permitting one to calculate the extent of glomerular filtration, Shannon²¹ suggestively indicated it to take place in dogs in that his experiments with urea given intravenously showed ratios of urea clearance to creatinine clearance essentially similar to some in which high urine flows were obtained by other means, but no data are presented indicating the concentration of urea in the blood reached in these experiments, and Goudsmit (The Renal Excretion of Inorganic Sulfates, Thesis, University of Minnesota Graduate School, 1939), on the basis of a limited number of experiments on dogs, was unable to recognize the concentration of urea (up to 100 mg per one hundred cubic centimeters of plasma) as a factor determining its rate of excretion when this was compared with that of creatinine

Peterson²³ reported approximately identical clearances of inorganic sulfate (5 cc), urea (5 cc) and sucrose (6 cc) in a case of diffuse arteriolar disease with hypertension and severe renal insufficiency²⁴ Generally speaking, the decrease of clearance of sulfate (in absolute numbers) would be less than that of urea, since the former starts at a lower level Thus "endogenous" inorganic sulfate clearance numerically appears to undergo smaller changes than either urea clearance or inulin clearance when renal function goes from "100 per cent" down to low levels Thus, as an index of glomerular filtration it would seem the least desirable of these three indexes of renal function

Mechanism of Sulfate Retention—The retention of sulfate in the body fluids, presupposing a normal metabolism of sulfur as such, theoretically can take place (1) through diminished glomerular filtration and (2) through increased tubular reabsorption

1 In the group of cases in which the values for serum sulfate were within normal limits, 46 per cent of the patients showed urea clearances exceeding 50 cc per minute, whereas of those with values for serum sulfate above 50 mg per hundred cubic centimeters only 29 per cent had a normal value for urea clearance Thus, in view of the established relation between urea clearance and the rate of glomerular filtration, it would appear that one of the factors responsible for the retention of sulfate in the body fluids is the diminution of glomerular filtration Nevertheless, in a large number of cases the estimated magnitude of glomerular filtration appears sufficient for adequate elimination of inorganic sulfate, and thus tubular reabsorption would appear to be in part responsible for its retention But the experimental data appear insufficient to incriminate an actual excess of tubular reabsorption for the retention of sulfates

2 The only conditions that we are aware of at the present time in which increased tubular reabsorption may be active in causing sulfate retention are the toxemias of pregnancy Anderson and Tompsett²⁵ found the inorganic sulfate content of serum to be normal in cases of normal pregnancy, but increases were observed in nearly all cases of eclampsia, even though the concentration of urea in the blood was still

23 Keith, N M, Power, M H, and Peterson, R D The Renal Excretion of Sucrose When Injected Intravenously in Man, *Am J Physiol* **105** 60-61 (July) 1933

24 These findings were presented at the meetings of the American Physiological Society at Cincinnati in 1933 They do not appear, however, in the printed abstracts published in the *American Journal of Physiology*

25 Anderson, D F, and Tompsett, S L Observations on the Inorganic Sulphate Content of the Blood in Eclampsia, *Brit J Exper Path* **13** 130-132 (April) 1932

normal. Similarly, Hunt and Wakefield²⁶ found the concentration of sulfate in the serum of 29 patients with preeclamptic toxemia to be increased in 22 (76 per cent), in none of these did the concentration of urea exceed 46 mg per hundred cubic centimeters of blood. The possibility, therefore, would appear to exist (until either confirmed or refuted by future experimental evidence) that sulfate retention in these cases actually was due to the relatively increased tubular reabsorption.

The clinical picture of the toxemias of pregnancy is complicated. However, in many cases these conditions have definite features in common with diffuse arteriolar disease with hypertension groups 3 and 4. This, in turn, suggests that the retention of sulfate might be due in part, at least, to vascular disturbances.

Why Does Sulfate Tend to Accumulate in the Body Fluids Earlier than Does Urea?—The recent communication by Wakefield, Power and Keith (1939) presents data on a group of 651 persons whose renal function was subjected to various tests. Of this number, 22 per cent showed retention of urea, as compared with 30.4 per cent having an excess of sulfate in the serum. In addition, of all patients with increased values for blood urea, 79 per cent also had retention of sulfate, whereas of all patients with increased values for serum sulfate, only 57.1 per cent had retention of urea. These data prove beyond any doubt that, statistically speaking, there is retention of sulfate before there is retention of urea. Although the final explanation for this phenomenon will have to await further study of the comparative rates of excretion of each of these substances during twenty-four hour periods, we believe that the following tentative calculations may be helpful in explaining the difference between the patterns of excretion of these two end products of protein metabolism.

Normally, the ratio of nitrogen to sulfur in the urine varies between 13 and 16, averaging approximately 15. Since approximately 88 per cent of the sulfur excreted is in the form of inorganic sulfate and since urea is responsible for between 80 and 90 per cent of all nitrogen excreted, it may be stated tentatively that the ratio of urea nitrogen to inorganic sulfate sulfur in the urine should be not far from 15. In the blood at the upper limit of normal there is present $28/60 \times 46 = 21.5$ mg urea nitrogen, and $32/96 \times 5.0 = 1.67$ mg of inorganic sulfate sulfur, per hundred cubic centimeters of serum. Thus the ratio of urea nitrogen to sulfate sulfur in the blood equals 21.5/1.67, or approximately 13. Thus, in order to be able to excrete sulfate as readily as it does urea, the kidney would have to maintain a ratio of sulfate clearance

²⁶ Hunt, A. B., and Wakefield, E. G. Concentration of Serum Sulfate During Pregnancy and in Pre-Eclamptic Toxemia, *Am J Obst & Gynec* **38** 498-501 (Sept.) 1939.

to urea clearance of 13/15, or 0.87. Normally, according to Keith, Power and Peterson,²⁷ this relation is approximately 0.50, and in our series, which, with a few exceptions, consists of cases of known renal or vascular disease, for all patients in whose cases a value for serum sulfate not exceeding 5 mg per hundred cubic centimeters was noted the ratio of sulfate clearance to urea clearance amounted to 0.65. Since in order to prevent sulfate retention as efficiently as urea retention a ratio of 0.87 should be maintained, accumulation of sulfate before accumulation of urea is to be expected in a significant number of instances.

The Term "Renal Insufficiency"—Renal functional activity appears to be sufficient as long as the products that the kidney is supposed to eliminate do not accumulate in the body fluids above the highest acceptable limits of normal concentration. As soon as accumulation above such a concentration takes place, renal function appears insufficient, and renal insufficiency, etymologically speaking, is present. There appears to be a certain hesitancy of some authors in using this expression, and thus the word "azotemia" is frequently employed to indicate the presence of an increased amount of urea nitrogen or nonprotein nitrogen in the blood. Since sulfate in an appreciable number of instances does accumulate before urea does, "renal insufficiency" would appear the more inclusive expression and, while conveying the same idea, leaves room for the discovery of other non-nitrogenous materials accumulating in the blood in renal disease before there is an increase in the concentration of urea.

Clinical Interpretation of Increased Serum Sulfate—It would seem worthy of a special analysis to attempt to ascertain whether the increase of the concentration of sulfate in the serum by itself has any particular clinical meaning. Thus, we thought it worth while to make a special study of those patients who showed normal values for blood urea, clearance and sulfate clearance and still had values for serum sulfate exceeding 5.0 mg per hundred cubic centimeters. In the present series 5 instances of the kind were observed (cases 42, 3, 29, 49 and 47, table 4). We are able to report on the subsequent history of all of them. One patient (case 47) with diffuse arteriolar disease with hypertension group 4, or so-called malignant hypertension, was dead within three months, 1 other patient (case 49) died eleven months after his examination. Of the other 3 patients, 1 (case 42), at the end of the day in which the clearance test was performed, came down with bronchopneumonia, however, five days later, after the fever had subsided, the concentration of serum sulfate had returned to within normal limits (4.2 mg per hundred cubic centimeters). This patient and the 2

²⁷ Keith, N. M., Power, M. H., and Peterson, R. D. The Renal Excretion of Sucrose, Xylose, and Inorganic Sulphates in Normal Man. Comparison of Simultaneous Clearances, *Am J Physiol* **108** 221-228 (April) 1934.

remaining ones were heard from between eight and sixteen months after the values for serum sulfate had been found to be elevated and were in a satisfactory condition. Thus, in the individual case no conclusions of prognostic significance can be drawn from the isolated finding of an increased concentration of inorganic sulfate in the serum.

Urea, sulfate, phosphate, creatinine, uric acid and many other more or less well defined compounds are among the products known to accumulate in the blood in the presence of failure of renal excretory function. Sometimes one appears to be retained much earlier than, or in considerable excess of, others. The clinician is aware that in the individual case the result of a single test does not adequately portray the finely differentiated picture of renal function. Thus, knowledge of the excretion of more than one substance, such as urea, is desirable, and the results of the present study appear to corroborate the findings of previous authors, indicating the definite usefulness of determination of the inorganic sulfate content of the serum.

TABLE 4—*Retention of Sulfate as the Only Sign of Renal Insufficiency*

Case Number	Serum Sulfate, Mg per 100 Cc	Sulfate Clearance, Cc /Min	Blood Urea, Mg per 100 Cc	Urea Clearance, Cc /Min
42	6.0	78.0	34	75.0
3	5.7	43.8	39	67.6
29	5.6	49.0	20	69.6
49	5.5	58.0	46	86.4
47	5.1	28.2	40	60.3

SUMMARY AND CONCLUSIONS

Comparative studies of blood urea, urea clearance, serum sulfate and sulfate clearance were performed on 50 patients. The majority were suffering from diffuse arteriolar disease with hypertension of various degrees of severity, most of the remainder, from chronic glomerulonephritis and other diseases of the urinary tract. The selection of the patients was conducted in such a fashion that half of the group would have normal and the other half increased concentrations of sulfate in the serum.

The increased concentration of serum sulfate was found to occur in diffuse arteriolar disease with hypertension groups 3 and 4 in 4 of every 5 cases, the urea clearance, the value for blood urea and the sulfate clearance indicating renal damage with decreasing frequency. The correlation of renal damage sufficient to bring about actual retention of an end product of normal protein metabolism and hypertensive vascular disease severe enough to be associated with retinitis is significant. It is assumed that arteriolar disease may well be responsible for both the retinal and the renal changes.

Generally speaking, in the more severe degrees of hypertension, as contrasted with the milder forms, there is a far greater probability of retention of either urea or sulfate in the blood than of decreases in the renal clearance of these substances. In this respect the patterns of excretion of urea and of sulfate are essentially similar. However, whereas the association of retention of urea in the blood and a normal value for urea clearance was observed only in 1 instance, 12 instances were observed of increased serum sulfate in the presence of a normal value for sulfate clearance.

The increase of the concentration of serum sulfate itself is held responsible for this behavior, and an analogy is seen with observations on experimental animals as well as on human volunteers, in whom the intravenous injection of sodium sulfate leads to considerable increases in the value for sulfate clearance without significantly changing renal function otherwise. In accordance with the analogy drawn from these experimental observations, the ratio of sulfate clearance to urea clearance is significantly increased in the cases of those patients who have increased values for (endogenous) sulfate in the serum as compared to those with normal values for serum sulfate.

On the basis of the filtration-reabsorption theory the observations are discussed. A tentative explanation is offered of the fact that, statistically speaking, sulfate accumulates in the blood before there is retention of urea. Both diminished glomerular filtration and increased tubular reabsorption were taken into consideration as factors responsible for the sulfate retention. The latter mechanism may well play an important role in causation of the increased concentration of serum sulfate associated with the toxemias of pregnancy.

Thus, although conclusions of prognostic significance in renal disease should not be based on the value for serum sulfate any more than on any other single laboratory index, determination of this index is a valuable adjunct in appraising renal function, and the pattern of excretion of sulfate is of considerable interest to the student of renal and vascular disease.

PANCREATIC FUNCTION IN A CASE OF NONTROPICAL SPRUE

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There are only scattered references either to pancreatic function or to the use of pancreatic preparations in cases of nontropical or tropical sprue throughout the literature over a period of years. Among the early investigators of the enzyme test on external secretions of the pancreas in cases of sprue are Brown,¹ Ashford² and Castellani.³ More recently, Sokhey and Malandkar⁴ and Hernandez⁵ have written on this subject. Snell⁶ reported results in 1 of his cases. The results are conflicting, though the tests carried out according to more recently acceptable methods on "fasting duodenal contents" show normal or increased lipase activity, normal trypsin activity and normal or depressed amylase activity.

There is a great deal of criticism with regard to the methods used in this type of study and with regard to the value of these tests as an indication of actual pancreatic function. McClure and Jones⁷ and Ivy⁸

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1 Brown, T R. The Gastro-Intestinal Findings in a Case of Sprue with a Note on Treatment Based on These Findings, *Bull Johns Hopkins Hosp* **27** 289-291 (Oct) 1916, The Absence of Pancreatic Secretion in Sprue and the Employment of Pancreatic Extract in the Treatment of the Disease, *Am J M Sc* **161** 501-507 (April) 1921, A Note on the Administration of Pancreatic Extract in the Treatment of Sprue, *J Trop Med* **24** 90 (April) 1921

2 Ashford, B K. Certain Conditions of the Gastro-Intestinal Tract in Porto Rico and Their Relation to Tropical Sprue, *Am J Trop Med* **8** 507-538 (Nov) 1928

3 Castellani, A. Beneficial Action of Raw Pancreas in Certain Cases of Sprue. Insulin in Cases of Sprue Complicated with Diabetes, *J Trop Med* **28** 230-231 (June) 1925, Brief Notes on the Administration of Liver, Pancreas and Stomach Extracts in Sprue, *ibid* **33** 126 (May) 1930

4 Sokhey, S S, and Malandkar, M A. Pancreatic Function in Sprue, *Indian J M Research* **15** 921-933 (April) 1928

5 Hernandez, L G. Pancreatic Juice in Normal Individuals and in Sprue, Porto Rico *J Pub Health & Trop Med* **6** 209-216 (Dec) 1930

6 Snell, A M. Clinical Observations on Nontropical Sprue, *Arch Int Med* **57** 837-856 (May) 1936

7 McClure, C W, and Jones, C M. Studies in Pancreatic Function. The Enzyme Concentration of Duodenal Contents in Pathological Conditions Involving the Pancreas, Liver and Stomach, *Boston M & S J* **187** 909-923 (Dec 21) 1922

8 Ivy, A C. Certain Aspects of Applied Physiology of External Pancreatic Secretion, *Am J Digest Dis & Nutrition* **3** 677-682 (Nov) 1936

have written excellent reviews covering the subject of pancreatic function and the physiology of the external pancreatic secretion. Ivy has brought out the point that because of dilution with bile, duodenal juice and gastric fluid, too much emphasis cannot be placed on concentration of enzymes obtained by duodenal drainage, but that it would be of great value to be able to estimate the total output of enzymes over a period of time. He expressed the hope that a dye may be discovered, eliminated exclusively by the pancreas, which can be used in a test for volume of secretion. At the time of his report, more than one hundred had been used unsuccessfully in his laboratory.

Quantitative analyses of stools with special emphasis on partition of fats, as well as determinations of the wet and dry weight and of the total amount of fat eliminated per day furnish additional information with regard to intestinal digestion and therefore with regard to pancreatic function. The type of curve obtained with the dextrose tolerance test may supply additional information in an investigation of the pancreas. In the use of pancreatic preparations most authors have relied on subjective improvement in their patients as a criterion for evaluating their results. Examples of this may be found in the works of Brown¹ and Castellani.³ Silverman and his associates⁹ used pancreatin and raw ground pancreas orally and investigated the enzymes in duodenal contents. Their results indicate that the digestive power of the duodenal contents is increased by administration of pancreatic preparations by mouth.

Morphologic studies in cases of nontropical and tropical sprue have not contributed anything definite toward a further understanding of the mechanism of this disease, nor have any specific pathologic changes in the pancreas been found to be associated with this disease. Suarez,¹⁰ Fullerton and Innes,¹¹ Burgdorf and Barry,¹² Thaysen,¹³ Anderson and Lyall,¹⁴ Holst,¹⁵ Jeckeln¹⁶ and Rosenthal¹⁷ all referred to autopsy

9 Silverman, D. N., Denis, W., and Leche, S. A Study of the Effect Produced on the Enzyme Concentration of the Duodenum by the Oral Administration of Certain Commercial Pancreatic Preparations, *Am J M Sc* **170** 727-730 (Nov.) 1925

10 Suarez, R. Clinical and Hematological Review of Sprue Based on Study of One Hundred and Fifty Cases, *Ann Int Med* **12** 529-535 (Oct.) 1938

11 Fullerton, H. W., and Innes, J. A. A Case of Idiopathic Steatorrhea, with Multiple Nutritional Deficiencies, *Lancet* **2** 790-792 (Oct. 3) 1936

12 Burgdorf, A. L., and Barry, T. A. Nontropical Sprue, *J A M A* **112** 2508-2509 (June 17) 1939

13 Thaysen, T. E. H. Nontropical Sprue. A Study in Idiopathic Steatorrhoea, London, Oxford University Press, 1932

14 Anderson, A. G., and Lyall, A. Two Cases of "Fatty Diarrhea" with Special Reference to Nitrogen Metabolism, *Quart J Med* **2** 339-351 (July) 1933

studies in cases of sprue and reported no diagnostic morphologic lesions. Atrophic changes of the intestinal mucosa, decrease in weight of the viscera and decrease in subcutaneous fat are usually reported. Other changes in the intestines as described in some of these reports suggest that some associated pathologic condition, such as regional ileitis, may have been present. Whipple,¹⁸ Blumgart,¹⁹ Jarcho²⁰ and Reinhart and Wilson²¹ described a clinical syndrome highly suggestive of sprue, associated with deposits of fat and fatty acids in the intestinal and mesenteric lymphatic tissues and a relatively normal pancreas, and designated this by the term "intestinal lipodystrophy of Whipple."

A case of nontropical sprue is presented here in which the diagnosis was based on the findings to be described, which conform with the points for diagnosis brought out in the literature. Chronic recurring steatorrhea with bulky, foul-smelling stools, marked emaciation, glossitis, macrocytic anemia, multiple vitamin and mineral deficiencies, amenorrhea and nutritional edema were present. Further support for the diagnosis in the case reported here was obtained from roentgen evidence of edema of the jejunum, ileum and colon and from a flat dextrose tolerance curve. This syndrome is compatible with that described by Thaysen and Norgaard,²² Manson-Bahr,²³ Castle and his associates,²⁴ Corr,²⁵ Fairley,²⁶ Snell,⁶ Miller and Barker,²⁷ Mooie and his associates,²⁸

15 Holst, J. E. Ein in Danemark aufgetretener Fall von Sprue, *Acta med Scandinav* **66** 74-99, 1927.

16 Jeckeln, E. Zur Pathologie der einheimischen Sprue, *Virchows Arch f path Anat* **303** 393-405, 1939.

17 Rosenthal, H. Die Darmefunde bei der einheimischen Sprue, *Virchows Arch f path Anat* **298** 706-727, 1937.

18 Whipple, G. H. A Hitherto Undescribed Disease Characterized Anatomically by Deposits of Fat and Fatty Acids in the Intestinal and Mesenteric Lymphatic Tissues, *Bull Johns Hopkins Hosp* **18** 382-391 (Sept) 1907.

19 Blumgart, H. L. Three Fatal Adult Cases of Malabsorption of Fat, *Arch Int Med* **32** 113-128 (July) 1923.

20 Jarcho, S. Steatorrhea with Unusual Intestinal Lesions, *Bull Johns Hopkins Hosp* **59** 275-289 (Oct) 1936.

21 Reinhart, H. L., and Wilson, S. J. Malabsorption of Fat (Intestinal Lipodystrophy of Whipple), *Am J Path* **15** 618 (Sept) 1939.

22 Thaysen, T. E. H., and Norgaard, A. The Regulation of Blood Sugar in Idiopathic Steatorrhea (Sprue and Gee-Herter's Disease), *Arch Int Med* **44** 17-28 (July) 1929.

23 Manson-Bahr, P. H. On Tropical or Indigenous Sprue, *J Trop Med* **32** 118-119 (May) 1929.

24 Castle, W. B., Rhoads, C. P., Lawson, H. A., and Payne, G. C. The Etiology and Treatment of Sprue, *Arch Int Med* **56** 627-699 (Oct) 1935.

25 Corr, P. Intensive Liver Therapy in Sprue, *Ann Int Med* **9** 1182-1186 (March) 1936.

Bassett and his co-workers,²⁹ Brull and his associates³⁰ Hanes and McBryde,³¹ Bennett and his co-workers,³² Linder and Harris,³³ Aub and his associates³⁴ and Mackie and Pound³⁵

We feel that more than the usual number of tests yielding information with regard to pancreatic function have been carried out in this case of nontropical sprue and that more than the usual clinical trial has been given pancreatic preparations. Therefore a report of the case may be of interest.

REPORT OF A CASE

M. W., a 31 year old white woman, was admitted to the Billings Hospital on Oct 29, 1937. She had had a gradual onset of symptoms three years previously, in the fall of 1934. At that time there had been a loss in weight of 34 pounds (15.4 Kg.), which she had failed to regain, a marked loss of appetite, increasing weakness and voluminous, foul, pale tan stools, occurring typically three to six times before 11 a. m. and accompanied with cramping pains in the lower part of the abdomen and gaseous distention. She voided frequently and had burning on urination, associated with dull pain in the lower part of the lumbar region. The menses decreased in amount of flow and occurred at irregular intervals. She consulted a number of physicians, but no diagnosis was established and no successful treatment instituted.

26 Fairley, N. H. Tropical Sprue and Its Modern Treatment, *Brit. M. J.* **2** 1192-1194 (Dec 29) 1934, Tropical Sprue with Special Reference to Intestinal Absorption, *Tr. Roy. Soc. Trop. Med. & Hyg.* **30** 9-32 (June) 1936.

27 Miller, D. K., and Barker, W. H. The Clinical Course and Treatment of Sprue, *Arch. Int. Med.* **60** 385-414 (Sept.) 1937.

28 Moore, H., O'Farrell, W. R., Geraghty, J. A., Hayden, J. M., and Moriarty, M. A. Gee-Thaysen Disease. Idiopathic Steatorrhea in Adults and Adolescents, *Quart. J. Med.* **5** 481-516 (Oct.) 1936.

29 Bassett, S. H., Keutmann, E. H., Hyde, H. V., Van Alstine, H. E., and Russ, E. Metabolism in Idiopathic Steatorrhea. I. The Influence of Dietary and Other Factors on Lipid and Mineral Balance, *J. Clin. Investigation* **18** 101-120 (Jan.) 1939.

30 Brull, L., Lambrechts, A., and Barac, G. Sprue non tropicale, etude approfondie de quatre cas observes en Belgique, *Rev. belge sc. med.* **10** 457-531 (Oct.) 1938.

31 Hanes, F. M., and McBryde, A. Identity of Sprue, Nontropical Sprue and Celiac Disease, *Arch. Int. Med.* **58** 1-16 (July) 1936.

32 Bennett, T. I., Hunter, D., and Vaughn, J. M. Idiopathic Steatorrhea (Gee's Disease). Nutritional Disturbance Associated with Tetany, Osteomalacia and Anemia, *Quart. J. Med.* **1** 603-677 (Oct.) 1932.

33 Linder, G. C., and Harris, C. F. Calcium and Phosphorus Metabolism in Chronic Diarrhea with Tetany, *Quart. J. Med.* **23** 195-212 (Jan.) 1930.

34 Aub, J. C., Albright, F., Bauer, W., and Rossmeisl, E. Studies of Calcium and Phosphorus Metabolism in Hypoparathyroidism and Chronic Steatorrhea with Tetany, with Special Consideration of Therapeutic Effect of Thyroid, *J. Clin. Investigation* **11** 211-234 (Jan.) 1932.

35 Mackie, T. T., and Pound, R. E. Changes in the Gastro-Intestinal Tract in Deficiency States, with Special Reference to Small Intestine. Roentgenologic and Clinical Study of Forty Cases, *J. A. M. A.* **104** 613-618 (Feb 23) 1935.

In March 1935, after her marriage in January of that year, she again consulted a physician because of irregular menses, anorexia, excessive fatigue, frequency of urination and diarrhea. Her weight until late in 1934 had averaged 126 pounds (57.2 Kg) but at this time was only 92 pounds (41.7 Kg). Pulmonary tuberculosis, malignant tumor of the urinary bladder and amebiasis were considered by the physician. Roentgen examination of the chest, cystoscopic study, biopsy of material from the cervix, agglutination tests and examinations of the stool for parasites, pus and blood failed to establish any definite diagnosis. Laboratory examination revealed the value for hemoglobin to be 85 per cent. The erythrocytes numbered 4,400,000 and the leukocytes 9,600 per cubic millimeter of blood. The urinary sediment showed 15 to 20 leukocytes per high power field and many bacteria. The sputum was negative for tubercle bacilli.

The weight did not increase with a high caloric diet, and all the complaints were still present a year later, at which time she had not improved in any way, according to the physician's report.

For a year she had no medical supervision, and in March 1937 she appeared very anemic. The value for hemoglobin was 65 per cent. There were 2,750,000 erythrocytes and 6,700 leukocytes per cubic millimeter of blood. She first noticed a tendency to bruise easily about this time. She was treated with brewer's yeast and a preparation of liver (Jeculin), as well as with intramuscular injections of iron, arsenic and phosphorus. At the end of April the value for hemoglobin was 70 per cent and the erythrocyte count 3,270,000 per cubic millimeter of blood. On May 2 she was given 500 cc. of whole blood by direct transfusion from a compatible donor. On May 8 the value for hemoglobin was 70 per cent and the erythrocyte count 3,380,000 per cubic millimeter. For two months after this the patient felt better, and the weight increased to 104 pounds (47.2 Kg), although the diarrhea continued.

During hot weather, in July, the diarrhea became very severe, with liquid stools six to seven times daily, typically occurring before 11 a. m. In two weeks' time there was a loss of 12 pounds (5.4 Kg), so that the weight was 92 pounds (41.7 Kg), the lowest level reached since the initial loss of 34 pounds (15.4 Kg). Edema of the ankles was first noticed with this exacerbation of severe diarrhea. The skin of the legs became tense and painful, and a scaling, itching, weeping rash appeared on the outer aspects of both legs and thighs. In August the patient noticed stiffness and tingling in the fingers and some tingling of the legs after defecation. After a cold in September a severe pain developed under both scapulas and was made worse by movements of the spine. On her own initiative, for a month before her appearance in the clinic she had taken Armour's liver extract by mouth, with a resulting definite increase in appetite. At no time had her diet been particularly limited except that in an endeavor to avoid "acid foods" for a year she had eaten no oranges, lemons or grapefruit. Her daily menus had included meat, potatoes, cooked and raw fruits and vegetables, apples or bananas between meals and an occasional glass of milk, of which she was not fond.

The patient had always lived in Chicago and had worked for the same wholesale grocery company for fifteen years. Prior to her admission to the hospital she had been unable to work for days at a time on several occasions. She had visited in Alabama twice since her marriage in 1935. The past and family histories added no significant information.

On her admission to the Billings Hospital physical examination revealed her to be pale and underweight. Her height was 65 inches (165 cm). Her weight was 102 pounds (46.2 Kg). The skin was dry. There were scaling lesions on the flexor aspect of the right arm, at the elbow and on the left side of the neck. On

TABLE 1.—Laboratory Data Obtained at Weekly Intervals During First Period of Hospitalization *

Week of	Stool Analyses										Dextrose Tolerance				Blood Chemistry						Hematologic Studies						Therapy				
	Body Weight, Kg	Daily Wet Stool, Gm	Daily Dry Stool, Gm	Daily Fat Stool, Gm	Elimination, Gm	Fat, % Dry Weight	Fat Partition			Fasting Level, Mg/100 Cc	Magnesium Rise, Mg/100 Cc	Vehicle	Method of Administration	Plasma Proteins, Gm/100 Cc	Ca, Mg/100 Cc	P, Mg/100 Cc	Chlorides, mM/L	pH	CO ₂ , mM/L	Cholesterol, Mg/100 Cc	Hemoglobin	Red Blood Cells	Reticulocytes	Mean Corpuscular Volume	Mean Corpuscular Hemoglobin	Cell Volume	Pancreatic Preparations	Vitamins	Liver Extract	Minerals	
							Fatty Acids, %	Soap, %	Neutral Fats, %																						
10/26/37	42.3	1194	104.0	60.8	58.1	72.6	18.2	9.2	72	18	H ₂ O	Oral	4.96	6.6	5.5	109	7.5	23.1	86	9.4	2.90	101	41.8	29							
11/5/37	40.3																														
11/12/37	41.1																														
11/19/37	42.2	751	81.7	36.6	45.1	81.6	7.6	10.8	95	6	H ₂ O	Oral	5.23	7.2	3.0	104	7.4	23.3		12.5	3.26	0.1				Pancreatic juice					
11/26/37	41.1																														
12/3/37	41.1																														
12/10/37	41.8																														
12/17/37	42.2	735	82.2	26.5	32.3	69.3	5.5	25.2																							
12/24/37	41.4																														
12/31/37	44.6																														
1/7/38	43.9	554	91.0	32.4	35.6	71.2	11.1	17.7	102	19	H ₂ O	Oral	5.51	8.6	3.5					10.8	3.15	2.4									
1/14/38	44.6																														
1/21/38	45.6	556	92.6	39.6	42.8	77.6	7.2	15.2																							
1/28/38	47.5																														
2/1/38	48.2																														
2/11/38	49.0																														
2/18/38	47.3	489	87.0	36.8	42.3	79.5	8.2	12.3	96	40	H ₂ O	Oral	5.94							135	12.0	4.11	2.0	90	29.2	37					
2/25/38	47.3																														
3/1/38	48.7																														

* The patient was on a constant diet of 150 Gm of carbohydrate, 85 Gm of protein and 141 Gm of fat

both legs and the outer aspects of the thighs were weeping, bleeding, scaling lesions with tense pitting edema of both legs extending from the ankles to the knees but not involving the feet. There were some carious teeth. There were a few aphthous lesions on the tongue and on the buccal mucosa. The tonsils were enlarged and cryptic. The blood pressure was 78 systolic and 54 diastolic, with tingling and stiffness of the fingers after application of the sphygmomanometer cuff for less than one minute. The lower portion of the abdomen was greatly distended. There was no rigidity. No masses were observed. Tenderness and rigidity on motion were elicited over the lower dorsal segments of the spine. Clubbing of the fingers and toes was observed. Examination otherwise gave essentially negative results.

During the first stay in the hospital, from Oct 29, 1937 to March 4, 1938, the patient was maintained on a diet of 150 Gm of carbohydrate, 85 Gm of protein, and 141 Gm of fat (table 1). Immediately prior to the quantitative collection of two day specimens of stool, a constant research diet of the same value was given the patient. Her weight increased 6.4 Kg during this stay in the hospital, after an initial loss of 2 Kg at the time when the edema of the extremities disappeared. Analyses of the dry stools by the method of Bloor³⁶ were carried out by Dr. H. A.

TABLE 2—*Enzyme Determinations on Duodenal Contents with the Patient Fasting*

	Time of Lipase Action	Time of Trypsin Action	Gm of Maltose Converted by Amylase
<i>11/16/37</i>			
Without stimulation	Less than 2¼ min	12½ min	0.25
With stimulation	Less than 2 min	4½ min	0.18
<i>1/27/38</i>			
Without stimulation	1 min 40 sec	7 min	0.55
1st specimen after stimulation	10 sec	4½ min	0.57
2d specimen after stimulation	25 sec	3 min	0.56

Trangsrud before, during and after administration of 500 cc of pancreatic juice daily by duodenal tube, divided into three doses and given one-half hour after meals. The pancreatic juice was provided through the courtesy of Dr. Lester Dragstedt of the department of surgery of the University of Chicago and was obtained from dogs with pancreatic fistulas prepared by his method³⁷. The stools decreased in number and weight during the whole stay in the hospital but the diminution was most marked in the periods of administration of pancreatic juice. Immediately before the pancreatic juice was given in both instances, enzyme determinations (table 2) were carried out on "fasting duodenal contents" by the method of Lueders³⁸ as modified by Hollander³⁹. In each of the two tests the activity of lipase was increased and that of trypsin and amylase was normal.

36 (a) Bloor, W. R. The Determination of Small Amounts of Lipid in Blood Plasma, *J Biol Chem* **77** 53-73 (April) 1938. (b) Man, E. B., and Gildea, E. F. A Modification of the Stoddard and Drury Titrimetric Method for Determination of the Fatty Acids in Blood Serum, *ibid* **99** 43-60 (Dec.) 1932.

37 Dragstedt, L. R., Montgomery, M. L., and Ellis, J. C. A New Type of Pancreatic Fistula, *Proc Soc Exper Biol & Med* **28** 109-110 (Nov.) 1930.

38 Lueders, C. W. Quantitative Estimation of Enzyme Concentration in Duodenal Fluids, *Am J Digest Dis & Nutrition* **2** 224-229 (June) 1935.

39 Hollander, E. A Clinical Method for Quantitative Determination of Pancreatic Ferments in Duodenal Contents, *J Lab & Clin Med* **16** 460-465 (Feb.) 1931.

The daily elimination of fat in the stools showed a definite decrease but remained higher than the normal average of 10 per cent to 25 per cent of the dry weight in twenty-four hours. The maximum decrease occurred after administration of pancreatic juice. The partition of fats remained relatively constant in all determinations, the level of fatty acids and that of soaps being higher than the normal average of 32 per cent and 26 per cent respectively and the neutral fraction being below the normal average of 42 per cent.

Flat dextrose tolerance curves were obtained in all tests in which dextrose was administered orally. A rise of 40 mg and more per hundred cubic centimeters was obtained when the dextrose was placed directly in the duodenum by tube, whether the vehicle was pancreatic juice or water.

The blood pressure averaged between 70 and 80 systolic and 50 to 55 diastolic throughout this period of observation. A Trousseau sign could be elicited at any time after the tourniquet or blood pressure cuff was in use for more than a minute, and the patient always walked stiffly and complained of numbness and tingling in the hands and feet. Without specific calcium therapy the calcium values rose slowly over a period of weeks from 6.6 mg to 8.6 mg per hundred cubic centimeters, without definite change in the mild symptoms of tetany mentioned. All determinations of the level of phosphorus gave normal values, varying from 3.0 to 5.5 mg per hundred cubic centimeters. The plasma proteins were at edema level of 4.96 Gm per hundred cubic centimeters on admission and did not exceed 5.94 Gm per hundred cubic centimeters at any time. The values for blood cholesterol were low on admission and rose to low normal values at the time of discharge.

Slight reticulocyte response occurred while pancreatic juice was being used. The values for hemoglobin did not exceed 13 Gm per hundred cubic centimeters, but the erythrocyte count rose steadily from a "low" of 2,730,000 to 4,110,000 per cubic millimeter. The mean corpuscular volume decreased from 101 microns to 90 microns and the value for mean corpuscular hemoglobin from 41.8 to 29.2, while the cell volume per cent increased from 29 to 37.

Culture of the stool was negative for *Monilia* after eleven days. Gastric analysis with an Ewald test meal gave normal results. The urea clearance was normal. Tests of hepatic function with bromsulfalein and galactose revealed no abnormality. The icterus index was 13. A fat tolerance test when the testing material was given either in water or in pancreatic juice yielded a flat curve. The biophotometric test showed normal light adaptation. The test for parathyroid hyperfunction gave a rise of 0.5 millimols per liter in rabbit serum, which is equivalent to a positive reaction, indicating normal function.

Proctoscopic examination revealed no abnormality. The basal metabolic rate varied from +2 per cent to -17 per cent. Roentgen examination showed no evidence of pancreatic stone or of osteoporosis, a normal esophagus, stomach and duodenal bulb and diffuse edema of the mucosa of the jejunum, the terminal portion of the ileum and the colon, associated with diffuse dilatation of the colon. An electrocardiographic tracing showed evidence of myocardial damage.

There was one elevation of temperature to 101 F for three to four days, during which time the urine was loaded with leukocytes and on culture yielded *Bacillus coli*. The urine became normal after administration of sulfanilamide, 1 Gm daily for two days, followed by ammonium chloride, 12 Gm daily for two weeks, and mandelic acid, 16 cc for ten days.

The patient was discharged from the hospital with no medication and instructed to eat a general diet without limitation. She gained weight at home, but the

stools became more frequent and were accompanied by some abdominal cramps and distention. After two weeks at home the patient complained of increasing numbness and tingling in the hands and feet, with loss of appetite and generalized weakness. A week later (March 24) she was readmitted to the hospital because of continued numbness and tingling of the extremities and loss of the voice after drinking cold water (table 3).

There had been a gain of 3 Kg during this interval, but the hemoglobin level had decreased almost 2 Gm to an admission value of 10.3 Gm, while the erythrocytes numbered 3,840,000 per cubic millimeter. The value for plasma proteins was 6.18 Gm, that for calcium 6.22 mg and that for phosphorus 2.8 mg per hundred cubic centimeters. There was a further drop in calcium to 5.86 mg per hundred cubic centimeters. For three weeks the patient was given vitamin B complex in the form of 45 Gm of vegex (an autolyzed yeast extract) daily. The reticulocytes did not exceed 0.2 per cent, and the hemoglobin dropped to a low of 9.8 Gm. Liver extract was then given intramuscularly in the form of Lederle's concentrate, 1 cc daily for seventeen days. The reticulocytes rose to 4.2 per cent, the value for hemoglobin to 12.2 Gm and the erythrocyte count to 4,050,000 per cubic millimeter. Lilly's liver extract, 3 cc intramuscularly daily for three weeks, was used, during which time the reticulocytes did not exceed 2.2 per cent, and the concentration of hemoglobin was no more than 12 Gm, while the erythrocyte count rose to 4,270,000 per cubic millimeter. The patient regained her appetite, her weight increased another 2.5 Kg during this time, and the value for calcium rose to 8.4 mg per hundred cubic centimeters. The patient menstruated for the first time in more than a year.

Elimination of fat in the stools increased from a daily output of 24.3 Gm just preceding the use of liver to 57 Gm per twenty-four hours after more than five weeks of daily injections of liver. At the time at which injections of liver extract were reduced to weekly intervals, 0.8 Gm of ferrous sulfate was given by mouth daily. At the time of discharge from the hospital the patient's blood pressure remained low, the systolic level being not above 80 and the diastolic no higher than 60. The electrocardiogram showed no further change. The appetite was excellent, the stools were semiformal, occurring once to twice daily, the body weight on discharge was 51.4 Kg. The patient moved about much less stiffly than at the time of admission. She was sent home to observe the following regimen: a diet of approximately 150 Gm of carbohydrate, 85 Gm of protein and 141 Gm of fat, three capsules containing vitamins A, B and D daily, 75 mg of vitamin C daily, 3.6 Gm of vitamin B as brewer's yeast daily, 3 Gm of calcium gluconate daily, and 0.2 Gm of ferrous sulfate daily. She was to return to the clinic at weekly intervals to receive intramuscular injections of 1 cc of Lederle's liver extract concentrate.

During an eight month interval in the clinic the patient maintained her weight well, had alternate periods of formed stools and watery diarrhea and complained of loss of appetite during hot weather. Administration of pancreatic substance (Armour's pancreatin), 4 Gm daily, was started on August 21, after which the appetite improved. During October and November liver was given twice a week because of continued intervals of diarrhea and abdominal cramps. Use of pancreatic substance was discontinued on December 12, because it was unobtainable until December 21, when its administration was resumed at the previous level of dosage. The patient lost her appetite within three days of the time pancreatic substance was discontinued and regained it almost immediately after the preparation was given again. In anticipation of rehospitalization, administration of liver

TABLE 3—Laboratory Data Obtained at Weekly Intervals During Second Period of Hospitalization¹

[illegible]

*The patient was on a constant diet of 150 Gm of carbohydrate, 85 Gm of protein and 141 Gm of fat

TABLE 4—Laboratory Data Obtained at Weekly Intervals During Third Period of Hospitalisation *

Week of	Stool Analyses										Dextrose Tolerance				Blood Chemistry						Hematologic Studies					Therapy			
	Body Weight, Kg	Daily Wet Stool, Gm	Daily Dry Stool, Gm	Daily Fat Elimination, Gm	Fat, % Dry Weight	Fat Partition			Fasting Level, Mg/100 Cc	Maximum Rise, Mg/100 Cc	Vehicle	Method of Administration	Plasma Proteins Gm/100 Cc	Ca, Mg/100 Cc	P, Mg/100 Cc	Chlorides, mM/L	pH	CO ₂ , mM/L	Cholesterol Mg/100 Cc	Hemoglobin	Red Blood Cells	Reticulocytes	Mean Corpuscular Volume	Mean Corpuscular Hemoglobin	Cell Volume	Pancreatic Preparations	Vitamins	Liver Extract	Minerals
						Fatty Acids, %	Soap, %	Neutral Fats, %																					
2/16/39	47.7							78	5	H ₂ O	Oral	5.54	6.8	1.9	106	7.32	21.0	98	10.5	3.10	2.0				B ₁ , C, D	Oral, 45 cc		Ca, Fe	
2/23/39	45.6																		10.0	3.60	1.6				B ₁ , C, D	Oral, 45 cc		Fe, Ca	
3/2/39	47.4	736	91.2	53.5	58.6	67.2	15.0	17.7					6.9	3.3					9.2	3.10	2.8				B ₁	Oral, 45 cc		Fe, Ca	
3/9/39	46.1											5.75	6.6	1.3	101			160	8.9	2.60	5.0	99.3	29.4	31		B ₁ , O	Oral, 60 cc		Fe, Ca
3/16/39	44.5											6.6	2.1						9.0	2.90	10.2				Comercial	IM, 3 cc			
3/23/39	46.7											6.1	1.5						9.5	3.40	3.6				B ₁ , O, IM, 3 cc	Comercial D		Ca, Fe	
3/30/39	47.0											6.5	1.5						9.1	3.30	2.3				O, D	Broiled		Fe, Ca	
4/6/39	47.6											5.7	2.5						9.1	3.47	3.0				B ₁ , D	Broiled		Fe, Ca	
4/13/39	48.8								86	14	H ₂ O	Oral	5.34	6.6	2.5				10.0	3.70	4.5				B ₁ , D			Fe, Ca	
4/20/39	47.8								92	16	After cortin (15 cc IM)		4.98	6.6	2.7	111			11.0	3.90	0.8	80.1	27.5	32		B ₁	Raw pulp		Fe, Ca
4/27/39	46.7								84	23	H ₂ O	Oral	5.95	7.5	2.6											B ₁ , D	concentrated		Fe, Ca
5/4/39	44.5																									B ₁ , D	concentrated		Fe, Ca
5/11/39	46.1	418.6	79.5	40.7	51.2	47.4	35.4	17.2					5.57	7.2	2.6				123	11.0	3.50				B ₁ , D	concentrated		Fe, Ca	
5/18/39	45.7	238.3	53.1	28.8	54.0	47.0	39.2	13.8																		B ₁ , D	concentrated		Fe, Ca
5/25/39	46.0	363.8	73.5	36.0	49.0	51.2	34.0	14.8																		B ₁ , D	concentrated		Fe, Ca
6/1/39	46.5												4.96	7.3	3.2											B ₂ , D	concentrated		Fe, Ca
6/8/39	47.5								83	38	H ₂ O	Oral	5.16	6.5	3.4											B ₁ , B ₂ , D	Comercial	Once	Fe, Ca
6/15/39	48.2																		12.0	3.97	1.0				B ₁ , B ₂ , D	Comercial	In 4 days	Fe, Ca	
																										B ₁ , B ₂ , D	Comercial	Once a week	Fe, Ca

* From 2/18 to 5/10 the patient was on a constant diet of 150 Gm of carbohydrate, 78 Gm of protein and 100 Gm of fat. From 5/11 to 6/20 she was on a constant diet of 155 Gm of carbohydrate, 175 Gm of protein and 92 Gm of fat.

extract was discontinued on Jan 7, 1939, and owing to an unavoidable delay the patient was not admitted to the hospital until February 16. By February 8 she had glossitis and was passing small, loose stools three to four times daily, with much abdominal distention. She had frequent nosebleeds and a number of subcutaneous ecchymoses.

On admission to the hospital (February 16) the patient weighed 47.7 Kg. The value for hemoglobin was 10.5 Gm. The erythrocyte count was 3,100,000 per cubic millimeter, with 2 per cent reticulocytes. The value for plasma proteins was 5.54 Gm, that for calcium 6.8 mg, that for phosphorus 1.9 mg and that for cholesterol 98 mg per hundred cubic centimeters of blood. Urinary excretion of ascorbic acid after administration of 480 mg of ascorbic acid intravenously was within normal limits. The patient was given 45 cc of a concentrated preparation of liver extract orally, vitamin C in 1,000 mg doses orally, vitamin B₁ intramuscularly, 30 cc of crude cod liver oil orally and 6 mg of calcium gluconate by mouth, all daily. She had acute abdominal distress with marked abdominal distention and rigidity, frequent loose stools and painful subcutaneous hematomas around the elbows and in the groins. The concentration of hemoglobin dropped to 8.9 Gm. The erythrocyte count was 2,600,000 per cubic millimeter. The mean corpuscular volume was 99.3, the mean corpuscular hemoglobin, 29.4, the bleeding time, two minutes, the clotting time, five minutes and the platelet count, 210,000. A quantitative analysis of the stool at this time by the Fowweather modification⁴⁰ of the Saxon method⁴¹ showed daily elimination of 53.5 Gm. of fat. All medication by mouth was discontinued on March 9, and within a few days the patient's general condition improved. The hemorrhagic manifestations disappeared, the abdomen became soft, and the stools became semiformed and less frequent.

The greatest reticulocytic rise obtained at any time occurred during the next few days, the value reaching of 10.2 per per cent. Daily intramuscular liver therapy, 3 cc of Chappel's concentrate (this was changed to 3 cc of Lederle's concentrate daily on April 20) was resumed on March 10 and continued throughout the stay in the hospital. By April 20 the concentration of the hemoglobin had reached 11 Gm, the erythrocyte count was 3,900,000 per cubic millimeter, with 0.8 per cent reticulocytes. The mean corpuscular volume was 80, the mean corpuscular hemoglobin, 27.5. Armour's pancreatic substance was given for a few days, and then its use was discontinued while fresh broiled whole pancreas, 200 Gm daily, was given for three weeks. The patient was unable to tolerate this diet, and so it was discontinued. Raw beef pancreas reduced to a pulp (100 cc) was given by duodenal tube for four days. The patient complained of loose stools and abdominal distress and was unable to tolerate this preparation.

Because of interest in Verzar's discussion of the relation of the adrenal cortex to intestinal absorption,⁴² dextrose tolerance determinations were made on three consecutive days, the second test being carried out after 15 cc of extract of adrenal cortex was given intramuscularly. There was no significant difference in the maximum rise in the level of blood sugar in the three tests. On the day after administration of adrenal cortex extract the blood pressure reading was the highest ever obtained, being 110 systolic and 65 diastolic.

40 Fowweather, F. S. The Determination of the Amount and the Composition of the Fat of Feces. I. Investigation of a "Wet" Method and Comparison with the "Dry" Method, *Brit J Exper Path* **7** 7-14 (Feb) 1926.

41 Saxon, G. J. A Method for the Determination of the Total Fats of Undried Feces and Other Moist Masses, *J Biol Chem* **17** 99-102, 1914.

42 Verzar, F. The Adrenal Cortex and Intestinal Absorption, *Am J Digest Dis & Nutrition* **4** 545-546 (Nov) 1937.

Calcium and iron by mouth were given again, beginning on March 23, and vitamin D in the form of drisdol (crystalline vitamin D in propylene glycol) (20 drops, or 5,000 U S P units of vitamin D) was given daily by mouth. Administration of these minerals and this vitamin D preparation was continued throughout the rest of the stay in the hospital.

The diet, which had approximate values of 150 Gm of carbohydrate, 78 Gm of protein and 100 Gm of fat, was changed to a high protein diet of 155 Gm of carbohydrate, 175 Gm of protein and 92 Gm of fat on May 11. The stools decreased in bulk, while the daily elimination of fat averaged 50 per cent of the dry weight, as determined by the wet method.

At the time of discharge the patient weighed 48.2 Kg. The value for calcium was 65 mg, that for phosphorus 34 mg, that for hemoglobin 12 Gm. The erythrocyte count was 3,970,000 per cubic millimeter, with 1 per cent reticulocytes. The patient was taught to weigh her own diet of 200 Gm of carbohydrate, 175 Gm of protein and 90 Gm of fat. The following daily medication was prescribed: calcium gluconate, 4 Gm; ferrous sulfate, 16 Gm; drisdol (crystalline vitamin D in propylene glycol), 20 drops; pancreatin, 4 Gm; and nicotinic acid, 10 mg. She returned to the clinic at weekly intervals to receive 3 cc of Lederle's liver extract concentrate and 50 mg of vitamin B₁ intramuscularly.

The treatment has continued as outlined until the present time. The patient's weight has averaged 48 Kg, the value for hemoglobin has varied from 11.4 to 12 Gm and that for blood calcium from 5.8 to 8.8 mg per hundred cubic centimeters. When she has had acute infections of the upper respiratory tract, none of which has been severe, she has lost as much as 10 pounds (4.5 Kg) in a week, but on recovery from the cold has regained that weight within two weeks. The stools become more frequent during these infections but of no greater volume. The patient has increased her activities greatly and is conscious of a sense of well-being which she had not experienced previously.

COMMENT

The greatest improvement in the condition of this patient occurred during the first period of hospitalization, when the therapy consisted only of administration of a constant diet with a fairly high fat content and of pancreatic juice. The stools decreased in daily wet and dry weight, in the per cent of fat present in the dry weight and in the total weight of the fat eliminated daily. The fact that the pancreatic juice brought about a more definite decrease than did liver extract alone is evidence that some factor of value in intestinal digestion, present in normal pancreatic juice, was deficient in this case. The partition of fat, with low values for neutral fat and high values for soaps and free fatty acids, is evidence of adequate fat splitting and poor absorption. Further evidence of normal pancreatic function is furnished by the values for nitrogen in the dry stool, which never exceeded 3.5 Gm daily, and by the results obtained from tests of "fasting duodenal content" on the mornings before the periods of administering pancreatic juice were started, in which values for proteolytic and amylolytic enzymes were normal and lipolytic activity was increased. These findings suggest that in this typical case of nontropical sprue there existed a deficiency in some pancreatic factor as yet undemonstrated. Similar results were

obtained by Triangsiud⁴³ in a study on totally depancreatized and totally depancreatized dogs with ligated ducts fed large quantities of pancreatic juice

In addition to the objective findings listed, the greatest subjective improvement occurred during the first period of hospitalization, after the use of pancreatic juice at a time when the stools were well formed and were passed at eighteen hour intervals. No comparable sense of well-being was experienced until the end of the third period of hospitalization, at which time the patient had been taking a high protein diet, a commercial pancreatic preparation, 3 cc of a liver preparation at weekly intervals, calcium and iron by mouth and vitamin B, D and C concentrates. The high protein diet was well tolerated by the patient and, in fact, conformed to her own tastes more satisfactorily than any other diet attempted. This diet is a possible factor both in stimulating external pancreatic secretion and in utilization of the liver extract.

With the use of dried pancreatic substance (Armour's pancreatin) an increase in appetite occurred, and when the preparation was discontinued for an interval anorexia appeared. The appetite was regained when use of the preparation was resumed. Pancreatic juice, which produced objective and subjective improvement, was not obtainable after the first period of hospitalization. On the other hand, raw pancreas in pulp form was not well tolerated, though given by duodenal tube.

When the dextrose used in the dextrose tolerance test was administered by duodenal tube with pancreatic juice as the vehicle instead of orally with water as the vehicle, it was at first thought that further proof of the value of pancreatic preparations had been obtained, because the maximum rise of the level of dextrose was 40 mg per hundred cubic centimeters, or more. These were the first normal values obtained. On repetition of the test, however, equal elevations resulted when the dextrose was given in water by duodenal tube. All subsequent tests in which the dextrose was given by mouth in water resulted in the usual flat curves.

The low values for blood calcium accompanied by normal or low values for inorganic phosphorus speak against hypoparathyroidism and appear to have been the result of high calcium excretion in the form of soaps in the stool or possibly of faulty intestinal absorption and increased rate of elimination of fecal material due to the diarrhea. The absence of active tetany may have been the result of the low levels of plasma protein and therefore of a decreased proportion of un-ionized calcium leaving ionized calcium values above the level of tetany. Alkalosis was not a factor, since the value for chlorides, the p_H and the carbon dioxide level were normal. Calcium and vitamin D administered orally over a long period brought the calcium toward normal levels.

43 Triangsiud, H. A. Personal communication to the authors.

The macrocytic hyperchromic anemia present at the first admission to the hospital gradually changed to a normocytic hypochromic type after pancreatic juice alone was administered. During a severe remission macrocytes reappeared, but the smear became normal after liver therapy. The reticulocyte response was greatest after oral administration of liver extract at a time when the hemoglobin concentration and the erythrocyte count were lowest.

The severity of the disease is indicated by the continued low levels of plasma proteins and calcium, by the low maintenance level of the hematologic picture, by the low dextrose tolerance curve and by the constant hypotension.

SUMMARY

A commercial pancreatic preparation, Armour's pancreatin, was a valuable adjunct in treatment in a case of severe nontropical sprue and had the advantages of being readily available and well tolerated by the patient.

Pancreatic function appeared normal as tested by enzyme determinations on "fasting duodenal content," partition of fats and low excretion of nitrogen in the stool.

The clinical improvement of the patient when pancreatin or normal pancreatic juice was supplied suggests that there exists in certain cases of severe nontropical sprue a deficiency in some factor as yet undemonstrated.

Normal pancreatic substance or juice appears to provide this deficient factor valuable in intestinal digestion.

NORMAL BLOOD PRESSURE

ALAN E TRELOAR, PH D

MINNEAPOLIS

A discussion of the range of normal blood pressures has been presented recently by Robinson and Brucer¹. The authors have wisely emphasized the need for more accurate standards in judging the normality of any blood pressure level shown on clinical examination. In the paper of reference they essayed to provide such standards, based on "an exhaustive statistical study of 7,478 men and 3,405 women selected at random". Disregarding the possible clinical soundness of their deductions, it cannot be agreed that their method of analysis of the data is statistically sound. The study appears to have been characterized both by biased selection of the basic data and by application of frequency curve probability values to distributions which certainly do not follow the function used. It is the purpose of this note merely to point out a few of the statistical errors that affect the validity of the conclusions. Unfortunately mere numbers of cases studied do not guarantee accuracy of the conclusions drawn.

It is well recognized in biostatistics that any attempt to fix limits of normal variation in a physiologic function is extremely hazardous. Nothing is more difficult to determine with satisfaction than the limits of range of a frequency distribution. When to this is added the confusing factor that the data under investigation represent a mixture of "normal" and "abnormal" values, there being no definition a priori of what constitutes physiologic normality, most fortunate conditions would have to prevail in order to make any thoroughly acceptable solution possible.

A brief consideration of the basic data is in order. Starting with a group of persons possessing life insurance and therefore originally selected by health criteria as good life insurance risks, the authors quickly passed to the statement that, because of time elapsed since the policies were issued, "our group comes close to being a typical portion of all age groups". Depending on the degree of closeness implied, one is led to the conclusion that the life insurance examination may have little value beyond perhaps rejecting those who are believed to be about

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1 Robinson, S C, and Brucer, M. Range of Normal Blood Pressure. A Statistical and Clinical Study of 11,383 Persons, Arch Int Med **64** 409-444 (Sept) 1939

to die. One may well feel hesitant about accepting so extreme a conclusion. But, independently of this point, one must recognize that voluntary appearance for a periodic health examination is not likely to yield a random sample of the population of insured persons in any one category. It seems idle to conjecture whether there is a balance between those who fear to come because of known or suspected ailments which might influence the results of future application for more insurance and those who, secure in their contracts, come for a check-up when they fear that all is not well. It seems doubtful, then, whether the basic material was not a badly biased sample as far as the general population is concerned. However, Robinson and Biucer stated that it "comes close to being a typical portion of all age groups between 20 and 70" and was taken under conditions of general health comparable to those of any random group in the total population."

It is in the statistical methods employed that the question of good reasoning comes most clearly into focus. After a thrust at the calculation of averages—"that most treacherous of statistical technics"—as normal values, they have sought shelter in modal values as better representations. One may well agree that averages are often misused, but does the "treachery" abide in the statistic any more than the blame for murder in the instrument employed to accomplish the end? The modal (or most frequently occurring) value is a useful element of descriptive information, to be sure, but a difficult one to determine objectively and with accuracy. Robinson and Biucer apparently used throughout their study an approximating expression which manages to shift the mode when a tail is cut away (or truncated) from the distribution. This is an obviously absurd result, for the value of most frequent occurrence is not affected by elimination of the values of comparatively rare occurrence.

In laying the ground for an arbitrary truncation of their distributions at 140 systolic and 90 diastolic to segregate the "abnormal" blood pressure groups, they gave the correlations of age with systolic and diastolic pressure for men as $+0.14 \pm 0.01$ and $+0.22 \pm 0.01$ respectively. The chances of such correlations arising solely through random sampling from an uncorrelated supply approach the infinitesimal, and yet they stated "Neither of the correlations for men is significant." One would suspect here a confusion between statistical significance and practical importance. An accompanying graph, however, shows that the *average* systolic pressure for 7,478 men rose from 118 mm at 35 years to about 148 mm at 85 years. One would not be disposed to regard such an average change in blood pressure with age as unimportant from the practical point of view, and it certainly is statistically significant.

It has been assumed by the authors, however, that this rise is due to the presence of hypertensive persons in the total group, and so a

rejection level of 140 systolic and 90 diastolic has been arbitrarily chosen for elimination of the "abnormals" The inevitable consequence is that the correlation between age and blood pressure is markedly reduced for the remaining persons But this reduction does not in itself constitute any justification whatever of the truncation It is merely a method of forcing a desired result It is not surprising, then, to read "The exclusion of pressures over 140 systolic and 90 diastolic does not alter the conclusions of the analysis" The conclusion preceded the truncation!

In discussing the "delimited group," accepted *pro tempore* as normal with respect to blood pressure, Robinson and Brucer set probability ranges of variation, assuming the statisticians' normal frequency function values to be appropriate This after arbitrary elimination of the upper 13 per cent of an obviously skew distribution! It has apparently been assumed that "normal" blood pressures follow the "law of error" distribution, which has unfortunately come to be known as the normal curve It should be pointed out that this is an assumption for which no proof is advanced, many physiologic variables show a skew distribution rather than a normal one But if the assumption is true in this case, the method used by the authors to estimate the parameters of the curve is altogether faulty in principle An erroneous type of reasoning with respect to application of normal curve probabilities which occurs repeatedly throughout the paper is well manifested by the sentence "With a standard deviation of 123 mm, it seems safe to conclude that the systolic blood pressures of this group of women, regardless of age, ranged from 100 to 125 mm" This is a range of one standard deviation on either side of the given mean During a first course in statistics the student learns that for practical purposes the range of the normal curve may be taken as plus and minus 3 standard deviations from the mean Plus and minus one standard deviation includes only 68 per cent of the cases, as the authors are apparently aware (p 416) A tabulation directly below the statement just quoted shows that 11 per cent of this selected group of persons had pressures either below 90 or above 130 mm By what conjuring does the range 100 to 125 mm come to embrace all?

Probably enough questions have been raised already to warrant abstinence from further indulgence along this line I wish to make it clear, however, that my objections to the paper of Robinson and Brucer do not center about the acceptability to physicians of the conclusions they have reached These may conceivably be reasonably sound in spite of the absence of satisfactory supporting evidence But to present such statistical manipulation as proof of the validity of the conclusions is to commit a serious offense against logical reasoning

NECROBIOSIS LIPOIDICA DIABETICORUM

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Necrobiosis lipoidica diabeticorum is a localized cutaneous lipoidosis, most often encountered in association with diabetes mellitus. It should be distinguished from the true xanthomas because of the absence of xanthoma or foam cells. Clinically the condition is characterized by papular or plaque-like lesions, usually on the lower parts of the legs. Microscopically it is characterized by the presence of necrotic foci which contain droplets of various lipoids which lie in the deep layers of the cutis.

HISTORY AND INCIDENCE

The first instance of this relatively infrequent condition was described by Oppenheim¹ in 1929. The case was one of diabetes mellitus in which the typical cutaneous lesions appeared several years after the onset of diabetes. Oppenheim named this new condition "dermatitis atrophicans lipoides diabetica." In 1932, Urbach² described a similar case in which the condition was likewise associated with diabetes mellitus, and gave the disease its present name. Since these first 2 reports, approximately 65 others have appeared in the literature more or less completely, whereas 11 additional cases have been mentioned in connection with the reports of the other cases. The first case reported in the United States was described by Zeisler and Caro³ in 1934. The first patient with this disease encountered at the Mayo

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1 Oppenheim Eigentümliche disseminierte Degeneration des Bindegewebes der Haut bei einem Diabetiker, Zentralbl f Haut- u Geschlechtskr **32** 179, 1929-1930

2 Urbach, E Beiträge zu einer physiologischen und pathologischen Chemie der Haut X Eine neue diabetische Stoffwechseldermatose Nekrobiosis lipoidica diabeticorum, Arch f Dermat u Syph **166** 273-285 (Sept) 1932

3 Zeisler, E P, and Caro, M R Necrobiosis Lipoidica Diabeticorum (Urbach), Arch Dermat & Syph **29** 167-169 (Jan) 1934

Clinic registered in 1936, and since that time 7 others have been studied here. The cases of these patients (to be described in this paper) together with those already reported in the literature represent a total of 86 which have been observed over the period of ten years since the first description of this condition. In addition to these 86 cases, which may be regarded as authentic, 8 others have been more or less completely described as examples of *necrobiosis lipoidica diabetorum* but have been eliminated from this study either because of incompleteness of the report or because of doubtful findings in their description. In 2 of these cases the cutaneous condition occurred in association with diabetes mellitus (1 of Michelson's cases and 1 reported by Feldman⁴). In Michelson's⁵ case cutaneous lesions were present at the site of injection of insulin and were not typical clinically of *necrobiosis lipoidica*. Feldman's case will be considered in detail further on in this report. In 4 of these doubtful cases the condition was not associated with diabetes mellitus. One, mentioned in connection with another case as observed by Chargin,⁶ is not described further. In 1 case, reported by Bruce-Jones,⁷ a microscopic picture much like that of a sclerosing type of sarcoid of tuberculosis was found. Giant cells were present, but lipid was not demonstrated in sections. In 1 case, originally reported by Jamieson⁸ as an example of *necrobiosis lipoidica* without diabetes mellitus, later there was found a blood sugar content of 225 mg per hundred cubic centimeters, this case has been included in our cases in which diabetes mellitus was present. The fourth case, that reported by Greenwood and Rockwood⁹ as an example of *necrobiosis* without diabetes mellitus, is not adequately described and hence is not included. Two other cases in which diabetes mellitus¹⁰ was present and 1 in which it was not present, described in the literature, are likewise doubtful.¹¹

4 Feldman, S. A Case for Diagnosis (*Necrobiosis Lipoidica Diabetorum*? *Xanthoma Diabeticorum* with Necrosis?), *Arch Dermat & Syph* **34** 326-328 (Aug) 1936

5 Michelson, H. E. *Necrobiosis Lipoidica Diabetorum*, *Arch Dermat & Syph* **34** 321-322 (Aug) 1936

6 Chargin, cited by Feldman⁴

7 Bruce-Jones, D. B. S. A Case Clinically Resembling *Morphoea* with a Tuberculous Background and Indeterminate Histology Suggestive of *Necrobiosis Lipoidica*, *Brit J Dermat* **49** 238-240 (April) 1937

8 Jamieson, R. C. *Necrobiosis Without Diabetes*, *Arch Dermat & Syph* **36** 912-913 (Oct) 1937

9 Greenwood, A. M., and Rockwood, E. M. *Necrobiosis Lipoidica Diabetorum*, *Arch Dermat & Syph* **35** 727-729 (April) 1937

10 Nanta, A., and Bazex, B. *Necrobiose dite lipoidique des diabetiques*, *Bull Soc franç de dermat et syph* **45** 827-831 (May) 1938

11 Hopkins, J. G., in discussion on Greenwood and Rockwood⁹

ETIOLOGY

In more than 87 2 per cent of all cases of this dermatosis, including both those encountered elsewhere and those observed at the Mayo Clinic, diabetes mellitus has also been present. All of our patients and 70 of the 78 patients whose condition has been reported elsewhere had diabetes mellitus at the time of their initial visit. However, as will be pointed out later in our study, in some cases the cutaneous lesions preceded the onset of diabetes by as long as eight years. Among the remaining 10 per cent of patients who had such cutaneous lesions, evidence of diabetes has not yet appeared.

The incidence of this condition among the total number of diabetic patients seen since 1929 is impossible to estimate, because figures on the incidence of diabetes in the population as a whole are not available. However, some conception of its rarity may be gained from a consideration of our figures at the Mayo Clinic. Since the first case of necrobiosis was encountered, in 1936, a total of 8 have been studied. In that same period, 2,000 cases of diabetes have been encountered at the clinic.

Aside from the high incidence of diabetes, examination has failed to reveal the presence of any predominant associated disease which might have etiologic significance. Among the nondiabetic patients presenting these lesions, a fairly high incidence of vasomotor instability and hypertension (Boldt¹²) and 1 patient with a background of tuberculosis have been found. Among the patients who had diabetes, only 1 with active pulmonary tuberculosis and only 4 with positive tuberculin reactions have been described in the literature, although several have had hypertension. Tuberculosis was eliminated as a possible diagnosis in all of our cases. In only 1 case in the entire series was a positive Wassermann reaction obtained.

In connection with the etiology, there must also be considered the influence of the age of the patient at the time of onset of the lesions, sex, race, the duration, severity and degree of control of the diabetes, trauma at the site of the lesions, and, finally, the concentration of lipoids in the blood and tissues at the time of the first examination.

More than 80 per cent of all the patients with necrobiosis lipoidica were women. In 49 of the total of 78 cases reported in the literature the patients were women. Seven of the 8 patients seen at the clinic have been women. All of the patients in the entire series have been of the white race and of a wide variety of nationalities.

A study of the cases reported in the literature and those encountered at the clinic with regard to the age at which the cutaneous lesions first

12 Boldt, A. Zur Kenntnis der Necrobiosis lipoidica ("diabeticorum"), Arch f Dermat u Syph **179** 74-124 (May) 1939

made their appearance reveals that this disease is primarily one of young persons. The commonest age at which the cutaneous lesions appear seems to lie between 10 and 40 years. In the cases reported in the literature, the age at the time of onset of the lesions (in the 47 cases in which this age was noted) ranged between 5 and 72 years, the average being 35 years. In all of the cases at the clinic, the age of onset ranged from 5 to 58 years, the average being 31.9.

The distribution of the cutaneous lesions according to age at the time of onset among the cases described in the literature is represented in table 1.

The age distribution of the patients seen at the clinic was as follows: 1 was 5 years of age at onset of the cutaneous lesions, 4 were between 20 and 30 years of age and 3 others were 43, 52 and 61 respectively, making a total of 5 who had the disease before the age of 40 years.

TABLE 1—*Distribution of Cutaneous Lesions According to Age as Described in the Literature*

Age by Decades	Number of Cases	Percentage of Total Series
0-9	4	8.5
10-19	9	19.2
20-29	7	14.9
30-39	10	21.3
40-49	8	17.0
50-59	6	12.7
60-69	3	6.4
Mean age	33	Average age 35.0
Less than 40	30	63.8
More than 40	17	36.2

A closer study of these figures reveals that in about 64 per cent of all cases encountered elsewhere and in about 60 per cent of all cases encountered at the clinic, cutaneous lesions developed prior to the age of 40 years, that is, 62.2 per cent of all patients whose ages at the time of onset of the cutaneous lesions were recorded had these lesions before the age of 40 years. Of this group itself, 57.1 per cent had such lesions during the second and third decades of life.

A study of the ages at the time of onset of diabetes mellitus and the ages at the time of onset of the cutaneous lesions revealed that although in the majority of the cases encountered elsewhere and at the Mayo Clinic the cutaneous lesions had developed after onset of the diabetes, in a certain small percentage of cases in both series the reverse was true. This relation between the onset of the diabetes and the onset of the cutaneous lesions may be seen from an examination of table 2.

Although in 55.6 per cent of the cases reported elsewhere diabetes was diagnosed one to ten years or more prior to the appearance of the cutaneous lesions (seventeen years in 1 of Boldt's cases), in 7 cases

in the literature, or in 17·8 per cent of the whole series (this includes only those cases in the literature in which the ages at the time of onset of diabetes and of the cutaneous lesions are given), a history of development of the cutaneous lesions prior to the onset of diabetes was obtained. Klaber¹³ described a case in which a history of cutaneous lesions dated back five years prior to the time of examination, without symptoms of diabetes but with a value for blood sugar of 300 mg per hundred cubic centimeters at the time of examination.

Michelson¹⁴ later reported a case in which cutaneous lesions appeared two years prior to the onset of diabetes. Bernstein¹⁵ reported a case in which there were symptoms of diabetes of eight years'

TABLE 2—*Relation Between Onset of Diabetes Mellitus and Onset of Cutaneous Lesions as Reported in the Literature*

Cutaneous Lesions Prior to Diabetes Mellitus			Simultaneous Onset		Cutaneous Lesions After Diabetes Mellitus		
Years Prior	Number	Per Cent of Total	Number of Cases	Per Cent of Whole Series	Years After	Number	Per Cent of Total
1	2	25·0	12	27·3	1	7	28·0
2	1	12·5			2	7	28·0
3	2	25·0			3	3	12·0
4	0	0·0			4	1	4·0
5	2	14·5			5	3	12·0
8	1				6	0	0·0
					7	1	4·0
					8	1	4·0
					9	0	0·0
					10 and greater	2	8·0
Totals	8		12			25	
Whole series, 45 cases							
Per cent of whole series		17·8					55·6
Average difference		42 months					40·3 months

duration but in which the cutaneous lesions dated back nine years. Gross and Machacek¹⁶ described a case in which the diabetes was discovered three years after the first appearance of the cutaneous lesions. Riehl¹⁷ reported a case in which the cutaneous lesions preceded the diabetes by three years. Boldt described 2 cases in which the cutaneous lesions appeared one and five years, respectively, prior to the onset of

13 Klaber, R. Necrobiosis Lipoidica Diabeticorum. Report of a Case, *Brit J Dermat* **46** 226-228 (May) 1934.

14 Michelson, H. E. Necrobiosis Lipoidica Diabeticorum, *Arch Dermat & Syph* **33** 900 (May) 1936.

15 Bernstein, J. C. Necrobiosis Lipoidica Diabeticorum (Urbach). Comparison with Granuloma Annulare, *Arch Dermat & Syph* **36** 282-286 (Aug) 1937.

16 Gross, P., and Machacek, G. F. Necrobiosis Lipoidica Diabeticorum, *Arch Dermat & Syph* **32** 491-494 (Sept) 1935.

17 Riehl, G., Jr. Necrobiosis lipoidica diabeticorum, *Zentralbl f Haut- u Geschlechtskr* **57** 11, 1937-1938.

diabetes Among those patients who had diabetes before the cutaneous lesions developed, the discovery of the former antedated the onset of the latter by an average of forty-two months Among those of whom the reverse was true, the cutaneous lesions preceded the diabetes by an average of forty and three-tenths months In 12 cases, representing 27.3 per cent of the whole series, the cutaneous lesions and the symptoms of diabetes were recognized at approximately the same time

Considering the series as a whole, the average duration of the cutaneous lesions at the time when the patient was seen was six and three-tenths years The duration of the diabetes at the time of the first examination ranged from several months to ten years, with an average duration of eight and six-tenths years Therefore, on the average the onset of diabetes mellitus preceded that of the cutaneous lesions by two and three-tenths years among all the cases

Of the 8 patients seen at the clinic, 5 had cutaneous lesions four months to three years after the onset of diabetes, an average of nineteen months In 2 cases the cutaneous lesions appeared one and two years, respectively, prior to the appearance of glycosuria In 1 of our cases diabetes and the cutaneous lesions appeared almost simultaneously Considering the entire series, the average duration of the cutaneous lesions at the time when the patient was first seen was four years The duration of diabetes at the time of the first examination ranged from several months to eleven years with an average duration of three and two-tenths years Therefore, on the average, the onset of diabetes preceded that of the cutaneous lesions by almost ten months

The severity of diabetes in the cases reported in the literature varied widely However, in more than 70 per cent it could be classified as moderately severe or severe Despite this fact, Hitch,¹⁸ in reviewing 20 of the cases reported prior to September 1937, made the statement that "apparently the condition [the necrobiosis] is not dependent on the severity of the diabetes or the extent of the hyperglycemia" In all of our cases the condition was classified as grade 3 (moderately severe), or grade 4 (severe) For all the cases in the literature the average value for "fasting blood sugar" on the first examination was 246.2 mg per hundred cubic centimeters, whereas for the cases observed at the clinic the average value on admission was 317.7 mg

Perhaps of more significance than the severity of the diabetes at the time when the patients were first seen is the factor of previous control of their disease In the majority of cases of necrobiosis lipoidica diabetorum, both those reported elsewhere and those encountered at the clinic, the course has been very poorly controlled throughout the disease In many cases histories of repeated episodes of acidosis

¹⁸ Hitch, J. M. Necrobiosis Lipoidica Diabetorum (Urbach and Oppenheim), *Arch. Dermat. & Syph.* **36**: 536-543 (Sept.) 1937

were obtained. All of our patients, with 1 exception, and most of those observed elsewhere had been treated with insulin during the greater part of their course. Some authorities have considered that the use of insulin may have had a role in the development of the cutaneous lesions. Michelson reported a case in which lesions developed at sites at which insulin had been injected. However, as has been mentioned, this was a very doubtful case of necrobiosis lipoidica. O'Leary, in considering 1 of the cases reported by Michelson,¹⁹ stated "Local reaction to injections of insulin at the same site may result in a gangrenous slough or simply in fatty necrosis without cutaneous gangrene, leaving depressed scars. This new entity (necrobiosis lipoidica diabetorum) may be the result of the use of insulin, in that the insulin, although not injected in the vicinity of the cutaneous lesions,

TABLE 3—*Relation Between Onset of Diabetes Mellitus and Cutaneous Lesions in Clinic Series*

Lesions Prior to Diabetes			Simultaneous Onset		Lesions After Diabetes		
Years Prior	Number	Per Cent of Total	Number of Cases	Per Cent of Whole Series	Years After	Number	Per Cent of Total
1	1	50.0	1	14.3	1	3	60.0
2	1	50.0			2	1	20.0
3					3	1	20.0
Totals	2		1			5	
Whole series, 8 cases							
Per cent of whole series		25.0	12.5				62.5
Average difference		1.5 years (18 months)			1.5 years (19 months)		

may produce vascular injury, or precipitate, in vessels already sclerotic, sufficient damage to result in this new cutaneous picture." In none of our cases did the lesions develop at the sites of injection of insulin. Furthermore, instances of allergic phenomena, such as urticaria, which might be traced to the injection of insulin have not been observed in any of the cases studied at the clinic and have not been reported in connection with any of the cases encountered elsewhere. Finally, as has been mentioned, in 8 instances among the cases reported elsewhere and in 2 of the cases encountered at the clinic the cutaneous lesions developed prior to the onset of diabetes mellitus. Also, in 8 cases in which there were typical lesions, evidence of diabetes was not found. Reaction to injection of insulin could have played no part in the development of the cutaneous lesions in these cases.

Trauma seems to play a definite role in the causation of this condition. From 12 to 16 per cent of the patients seen elsewhere and at least 1 of those studied at the clinic stated that some type of injury had

19 Michelson, H. E. Necrobiosis Lipoidica Diabeticorum, Arch. Dermat. & Syph. 30: 897-898 (Dec.) 1934.

occurred at the site of the cutaneous lesions prior to their development. Bruises, cuts, scratches and mosquito bites were noted among the preceding injuries. In 2 instances, lesions in the papular stage advanced rapidly to a state of ulceration after trauma.

Diet prior to onset of the cutaneous lesions is apparently not a factor of great significance. Only 3 of the patients in the entire series, 1 of them among those seen at the clinic, had been on a diet high in fat at some time during the course of diabetes. Most of the patients had been on a diet relatively high in carbohydrates prior to the onset of the cutaneous lesions. None of the patients seen at the clinic was overweight at the time of examination.

In 8 cases in which diabetes mellitus was not present, 7 reported by Boldt and 1 by Goldsmith,²⁰ there were cutaneous lesions which were identical grossly and microscopically with those seen in the cases in which diabetes was present, but there were no symptoms of diabetes, and on examination normal dextrose tolerance curves were found. Goldsmith reported a case in which the lesions, both clinically and histologically, were necrobiosis lipoidica and in which the Mantoux reaction was positive with a dilution of 1:10,000 (old tuberculin). There were no signs of active tuberculosis. Goldsmith also mentioned another case in which the lesions grossly resembled necrobiosis lipoidica but microscopically represented the picture of cutaneous tuberculosis. In this case a diagnosis of scleroderma-like erythema induratum was made. Goldsmith regarded this condition and necrobiosis lipoidica diabetorum as different phases of the same disease.

MORBID ANATOMY

The lesions described in the literature, as well as those observed in our cases, have followed, in general, a comparatively definite pattern both macroscopically and microscopically. Among the cases in the literature, complete descriptions of the lesions were given in 54 instances, with histologic descriptions in 35. In all of our cases we have descriptions of the gross appearance of the lesions, but in only 3 were there microscopic studies as well.

Grossly, these lesions may represent one phase of the disease or several at the same time. Usually the lesions are asymptomatic, although in some cases itching and burning have been complained of. The most common site of occurrence of these lesions is on one leg or both legs below the knees. In approximately 85 per cent of all cases reported elsewhere and in 82 per cent of our cases the lesions have occurred at this site. Bilateral lesions were present in approximately 54 per cent of the cases observed elsewhere and in 75 per cent of our

²⁰ Goldsmith, W. N. Necrobiosis Lipoidica, *Proc Roy Soc Med* 28:363-364, 1935.

cases In 6 of the cases reported elsewhere one or both arms were involved, whereas in our series 1 patient had involvement of the wrists In this case the legs also were affected Other sites of occurrence which have been reported include the thighs, abdomen, breasts and (in Oppenheim's case) almost the entire cutaneous surface From one to fifteen lesions have been reported in an individual case, but the average number of lesions found in each case among those reported elsewhere was five at the time of examination

According to Hitch, the typical lesions may go through four phases (1) a small, reddish, infiltrated papule, (2) an increasingly larger lesion which takes on a violaceous hue, (3) a slightly raised, firm yellow plaque, which may soften and sometimes may ulcerate and (4) a flattened, yellowish region with central atrophy and depression and a peripheral irregular scaling red or violaceous region of infiltration The color is due to the amount of lipoids deposited in the connective tissues, secondary deposition of hemosiderin and a variable amount of stasis in the underlying blood vessels

In the majority of the cases encountered elsewhere the course of the lesions followed this pattern closely The lesions usually started as firm papules and progressed to plaque formation with or without subsequent ulceration The plaques ranged from 1 by 2 cm to 3 by 5 cm In the course of months, many of these lesions became transformed into atrophic scars covered with fine scales In approximately a fourth of these cases the lesions were papules at the time of examination, in more than 50 per cent there were plaques, which were round, oval or irregular Among our cases, in 2 there were papular or nodular lesions, in 5, plaques, and in 3 depressed scars accompanying the other lesions The literature records depressed and atrophic scars in more than a third of the cases Ulceration of the lesions occurred in only a quarter of the total cases as compared with an incidence of 50 per cent among our cases In 2 cases reported in the literature, cultures of the material from these ulcers on ordinary mediums yielded negative results In 1 of our cases similar cultures yielded gram-positive cocci

Central xanthochromia has been observed frequently in the lesions of necrobiosis lipoidica In two thirds of the cases reported in the literature and in half of the cases encountered at the clinic this feature was present Likewise, a violaceous or reddish brown border is often found in these lesions, having been reported in almost 60 per cent of the cases in the literature and in 50 per cent of our cases, usually these borders are well defined The surface of the lesions showed dry, adherent scales in about 30 per cent of the cases in both series, and, in addition, telangiectasis of the surface occurred in 50 per cent of our patients as compared with an incidence of almost 45 per cent among

the patients seen elsewhere. Black central crusting was noted in 20 to 25 per cent of the cases in both series.

Histologic studies of these lesions revealed that the greatest changes occurred in the deep layers of the cutis. In almost half of the 21 cases in which microscopic studies were made there were minor changes in the epidermis, however, including hyperkeratosis, intercellular edema and flattening of the rete ridges. The granular layer, except in 1 instance, was intact throughout. In only 2 cases were there any changes in the papillary layer of this cutis, in these the changes consisted of a moderate amount of vascular dilatation and perivascular infiltration. Among the remaining cases, the entire pathologic change occurred in the subpapillary layers of the cutis.

The histopathologic picture is characterized by necrobiotic rather than true necrotic changes in the collagen fibers, consisting in homogenization and degeneration of the fibers together with loss of elastic tissue and a peripheral perivascular inflammatory reaction involving chiefly connective tissue cells, various types of histiocytes, lymphocytes and occasionally leukocytes and plasma cells. Varying degrees of obliterative change were encountered in the smaller blood vessels, which are surrounded by the infiltrate and thus account for the necrobiotic changes in the collagen fibers in the center of the plaques. Varying amounts of lipoids were observed, chiefly in the center of the lesions in the region of degeneration of the collagen fibers. These lipoids stained reddish brown with sudan III and did not show double refraction with the polariscope. Most authors feel that these lipoids are composed of phospholipids and free cholesterol. Most of the fat lies extracellularly, although occasionally small, intracellular deposits are seen in the chromatophores, without, however, their being typical xanthoma or foam cells, such as are characteristic of the usual types of xanthoma. Xanthoma cells were reported present in 1 case of necrobiosis by Feldman, but the diagnosis in this case was questionable, as the distribution and characteristics of the lesions were those of xanthoma diabeticorum. The patient had marked elevation of the concentration of lipoids in the blood, and the lesions involuted promptly under a proper dietary regimen and injections of insulin. In 2 cases²¹ reported in the literature as examples of necrobiosis lipoidica, extracellular double refracting crystals were found. In none of our 3 cases was this phenomenon observed. Giant cells were reported in 4 cases in the literature but were more of the foreign body type than of the Touton type of giant cell which is characteristic of ordinary xanthoma. Deposits of hemosiderin in the necrobiotic areas were a common finding in cases studied elsewhere, and they were a uniform finding in the 3 cases studied at the clinic.

21 Klaber, R. Necrobiosis Lipoidica Diabeticorum, Proc. Roy. Soc. Med. 30: 976, 1937.

DIAGNOSIS

It should be possible to make a diagnosis of necrobiosis lipoidica diabetorum on the clinical appearance of the lesions alone. The finding on the lower extremities of flattened plaques with yellowish centers surrounded by violaceous or red-brown borders, with or without central ulceration, especially in a known case of diabetes mellitus, is characteristic. These lesions differ considerably from those of the other types of xanthomatosis, which are usually firm, yellowish papules occurring on the extensor surfaces of all four extremities. The finding of intracellular deposition of lipoids in foam cells in the latter lesions makes recognition final. Xanthoma diabetorum is a typical xanthoma both macroscopically and microscopically, and the lesions, unlike those of necrobiosis lipoidica, can be made to improve rapidly by proper management of the diabetes.

Other necrotic lesions which occur in association with diabetes mellitus may be confused with necrobiosis lipoidica. Localized necrosis of the extremities may follow trauma to these parts in cases of diabetes mellitus. These lesions are usually solitary rather than bilaterally symmetric, are moist rather than dry and may be so deep that they involve the subcutaneous tissues. A spontaneous nontraumatic variety of localized necrosis may also occur in cases of diabetes mellitus. In this type the eruption may vary in bilateral symmetry and may appear as gangrenous patches of variable depth which are preceded by bullae or as small, dry gray or black gangrenous patches which involve hardly more than the corium and which, after several days, separate to leave a granulating, slowly healing surface. Microscopic examination of any of the lesions reveals destruction of all types of tissue in the involved regions, not the pseudonecrotic degeneration of the collagen fibers with complete loss only of the elastic fibers seen in cases of necrobiosis lipoidica. Furthermore, any of these lesions will heal with proper treatment of the diabetes.

Lipoid proteinosis is, like necrobiosis lipoidica, a form of extracellular xanthomatosis, and like necrobiosis lipoidica it tends to occur in association with diabetes mellitus. However, the clinical appearance of the lesions differs greatly from that seen in cases of necrobiosis. Also, the lesions often involve the mucous membranes in cases of lipoid proteinosis, never in cases of necrobiosis. Furthermore, patients who have the former disease have an increase of lecithin in the blood and tissues. Microscopically the two conditions differ in that in lipoid proteinosis there is a homogeneous lipid deposit in the connective tissue and around the blood vessels extracellularly, and there is not the marked necrosis of the connective tissue seen in cases of necrobiosis lipoidica.

The papular form of necrobiosis lipoidica may be confused with the reddish papules of so-called extracellular cholesterosis or of amy-

loidosis. However, one of us (Montgomery) believes that the former represents simply a fibrous end stage of xanthoma tuberosum, and foam cells can still be demonstrated in the lesions. The latter condition shows homogeneous masses in the papillary and subpapillary layers of the corium which give a positive stain for amyloid.

Granuloma annulare may be microscopically and even clinically similar to necrobiosis lipoidica. Bernstein studied sections of the lesions in 4 cases of granuloma annulare, 3 in which diabetes mellitus was ruled out and 1 in which diabetes mellitus had been present for eight years. The sections were stained with sudan III, and none of them showed sudanophilic droplets between the collagen fibers. This is contrary to what is usually true of necrobiosis lipoidica.

STUDIES ON PATHOGENESIS

Since this condition represents essentially a lipid disturbance of the skin, some alteration in the lipid content of the blood and tissues has been sought as a possible explanation for the appearance of these lesions. In 39 of the cases encountered elsewhere the cholesterol content of the blood has been determined, whereas in only 6 of these cases have complete studies of the blood lipids been made. In all of the cases seen at the clinic complete determinations of blood lipids have been made. Only 4 cases in the entire series, 2 at the clinic, 1 reported by Usher and Rabinowitch²² and 1 reported by Zeisler and Caro,²³ have been studied from the standpoint of the lipid constituents of the tissue itself.

Correlation of the values for blood lipids found elsewhere and those found at the clinic is difficult because of the different methods of analysis used. In many of the cases reported elsewhere older methods of analysis have been used, hence only approximate comparisons can be made with our figures.

In all of our cases the studies on the blood lipids were made in the morning, before the patients had had breakfast, and the procedures were carried out on plasma. In some of our cases older methods of analysis may have been used, but in most the cholesterol was determined by the methods of Bloor,²⁴ lecithin, in some instances by the method of Whitehorn²⁵ and in others, especially the more recent ones, by that

22 Usher, B., and Rabinowitch, I. M. Necrobiosis Lipoidica Diabeticorum. Report of a Case with Clinical, Pathologic and Biochemical Observations, *Arch Dermat & Syph* **35** 180-187 (Jan) 1937.

23 Zeisler, E. P., and Caro, M. R. Necrobiosis Lipoidica Diabeticorum, *Arch Dermat & Syph* **30** 299 (Aug) 1934.

24 Bloor, W. R. The Determination of Cholesterol in Blood, *J Biol Chem* **24** 227-231, 1916.

25 Whitehorn, J. C. A Method for the Determination of Lipid Phosphorus in Blood and Plasma, *J Biol Chem* **62** 133-138 (Nov) 1924.

of Youngburg and Youngburg,²⁶ and the total lipoids by the technic outlined by Bloor²⁷ The concentration of these same substances in tissue was estimated by the same procedures on the alcohol-ether extract of the tissues In all 4 instances in which a determination of the tissue lipoids has been made the figures for the various lipoids are given as percentages of the wet weight of the specimen In all instances, also, the subcutaneous fat and adjacent normal tissue were carefully trimmed from the necrobiotic nodule, and immediate analysis was made In the case reported by Usher and Rabinowitch the skin near the necrobiotic nodule was also studied chemically for comparison, in these instances also the subcutaneous fat was cut off before the analysis was made

The normal figures for blood lipoids in use at the Mayo Clinic at the time the blood and tissue analyses on our patients were made, as

TABLE 4—*Values for Lipoid Constituents*

Lipoid Constituents	Mg per 100 Cc Plasma		
	Older Figures (Montgomery and Osterberg)		New Figures (Barker) Average Mean Normal
	Range of Values	Average	
Total cholesterol	160 200	180	218
Cholesterol esters	110 145	125	154
Lecithin	200 250	225	223
Total fatty acids	335 350	345	350
Total lipoids	500 550	525	565

well as the figures recently determined at the clinic as the average mean normal values for the various lipoids, are given in table 4

The new figures given in this table represent the average mean normal values as found in recent studies conducted at the clinic on 200 presumably normal subjects by the committee on blood lipoids (Barker, Montgomery, Osterberg, Willius and Wilder) and are to be reported in a forthcoming paper by Barker²⁸ These studies have revealed an even wider variation in normal values for all the blood lipoids than did the older figures previously considered as normal values and, on the whole, higher values for the various lipoids in the third and fourth decades of life Further studies on blood lipoids are contemplated in regard to correlating the values not only with age groups but with sex and with the presence or absence of such complicating factors as obesity

26 Youngburg, G E, and Youngburg, M V Phosphorus Metabolism System of Blood Phosphorus Analysis, *J Lab & Clin Med* **16** 158-166 (Nov) 1930

27 Bloor, W R The Determination of Small Amounts of Lipid in Blood Plasma, *J Biol Chem* **77** 53-73 (April) 1928

28 Barker, N W The Plasma Lipoids in Arteriosclerosis Obliterans, *Ann Int Med* **13** 685-692 (Oct) 1939

and pregnancy It is worthy of note that the upper limits of normal given in the older set of figures closely approximate the new average mean normal figures

The normal figures for the lipoids of the skin likewise vary considerably For a complete review of the work done on tissue lipoids, reference may be made to a recent paper by Montgomery and Osterberg²⁹ These authors came to the conclusion that "the amount of total lipoids of the normal skin averages less than 3 per cent of the wet weight, that from 5 to 15 per cent of these total lipoids is in the form of cholesterol (most of it being in the free form), and that the lecithin varies from only a trace up to 30 per cent of the total lipoids" Table 5 represents a summary of values for the blood lipoids as noted both at the clinic and elsewhere

In the total series of cases studied elsewhere the only blood lipid which has been studied in a significant number of cases is cholesterol

TABLE 5—Summary of Values for Blood Lipoids

Lipoids	Average Mean Normal		Cases Seen Elsewhere			Cases at the Clinic	
	Older	New	Number	Range of Values	Average Value	Range of Values	Average Value
Cholesterol	180	218	39	129-720	271	131-248	210.5
Cholesterol esters	125	154	16	74-370	163	87-177	137
Lecithin	225	223	6	178-625	372	192-250	219
Fatty acids	345	350	11	421-657	559	269-500	346
Total lipoids	525	565	6	700-1,500	995	401-728	551

This was determined in 39 cases, and, as may be seen from table 5, the average value for this lipid constituent of the blood is somewhat, but not markedly, greater than our average mean normal values However, the significance of this finding is rather doubtful, as in only 2 cases of the entire series have cholesterol ester crystals been found in the lesions themselves, although, as will be shown later, in 2 of the 4 cases in which tissue lipid studies were made the values for tissue cholesterol were somewhat greater than normal In the clinic series, from which more accurate comparisons may be made, the average value for cholesterol was almost identical with the new average mean normal value as reported by Barker It is of interest to note that in 1 of the cases in which cholesterol ester crystals were observed in the lesions (Klaber), two estimates of the value for blood cholesterol were within normal limits, being 166 mg and 195 mg per hundred cubic centimeters respectively None of our patients have shown cholesterol ester crystals in the lesions Urbach³⁰ reported a patient

29 Montgomery, H, and Osterberg, A. E. Xanthomatosis. Correlation of Clinical, Histopathologic and Chemical Studies of Cutaneous Xanthoma, Arch Dermat & Syph **37** 373-402 (March) 1938

30 Urbach. Necrobiosis Lipoidica Diabeticorum, Dermat Wchnschr **99** 1596 (Dec 8) 1934

who on fundusoscopic examination was found to have glittering particles in both retinas, he thought that these particles might have been cholesterol

In the small number of cases reported in the literature in which complete studies of the blood lipoids have been made, all of the values for lipid constituents, besides cholesterol, have been elevated to a variable extent. The values for cholesterol esters have ranged from 74 to 370 mg per hundred cubic centimeters, with an average of 163 mg, those for lecithin, from 178 to 625 mg per hundred cubic centimeters, with an average of 372 mg, those for fatty acids, from 421 to 657 mg per hundred cubic centimeters, with an average of 559 mg, and those for total lipoids from 700 to 1,500 mg per hundred cubic centimeters, with an average of 995 mg. As has been pointed out, these figures are difficult to evaluate first, because of the variation in the types of analysis used, second, because the number of cases in which complete studies of the blood lipoids were made is small, and third, because the range in the values for each lipid constituent of the blood varies greatly with different methods of analysis and, as Barker has shown, also with the different age groups. Hence most of the figures given in the literature lie very close to the ranges of normal values. The values for blood lipoids in the case reported by Feldman have not been included in these calculations because, as has been mentioned, this was not clearly a case of necrobiosis lipoidica.

Marble³¹ has said that in 6 of 9 cases which he has encountered, none of which has been completely reported, at one time or another there were total cholesterol values above 230 mg per hundred cubic centimeters, but none higher than 312 mg. In all cases the ratio of cholesterol esters to total cholesterol was normal. In 2 instances the values for total lipoids were more than 800 mg per hundred cubic centimeters, and in these cases the phosphatide content of the blood also was elevated. In addition, Marble stated that there is usually a moderate increase in all of the lipid elements of the blood in cases of necrobiosis lipoidica but that the same degree of increase is also seen in cases of diabetes mellitus without necrobiosis.

The study on the blood lipoids in this condition at the clinic was done in all 8 cases. Also, complete quantitative analysis of the lipid constituents of tissue was made in 2 cases. As indicated in table 5, comparison of the average normal values for each of the blood lipoids as found in these 8 cases with the recently obtained average mean normal values of Barker reveals them to be almost identical. Furthermore, in every instance the range of values for the individual lipoids in these 8 cases corresponded very closely with the range of values for these lipoids for the same age groups among the normal subjects studied.

31 Marble, A., in discussion on Greenwood and Rockwood.⁹

by Barker and his co-workers. On the whole, therefore, it may be said that our studies of blood lipoids in cases of necrobiosis lipoidica have yielded negative results.

Although quantitative determinations of the lipoid constituents of the tissues have been made in only 4 cases, several investigators have made qualitative studies on sections from the lesions by means of selective staining. Michelson and Laymon,³² Balbi³³ and Zeisler and Caro²³ have reported that the fat droplets in these lesions consist of phospholipids and neutral fats. Usher and Rabinowitch²² have reported that in 1 case the free cholesterol found in the tissues was five times that found in normal skin.

The values for the tissue lipoids in the 4 cases in which they have been determined quantitatively are indicated in table 6. As in the case of the blood lipid determinations, the significance of the figures obtained

TABLE 6—*Values for Tissue Lipoids*

Lipoid Constituent	Usher and Rabinowitch		Clinic Case 1		Clinic Case 2		Zeisler and Caro	
	% Wet Weight	% Total Lipoids	% Wet Weight	% Total Lipoids	% Wet Weight	% Total Lipoids	% Wet Weight	% Total Lipoids
Cholesterol, total	2.20	26.5	0.43	20.9	0.30	2.21	0.554	8.9
Cholesterol, esters	0.19	2.3	0.40	19.4	0.20	1.48		
Cholesterol, free	2.02	24.3	0.03	1.5				
Phospholipids	0.24	2.9	0.13	6.3	0.044	0.324	0.397	6.4
Phospholipids as lecithin	6.00	72.3	3.20	155.3	1.10	8.09	9.930	159.0
Fatty acids			1.63	79.1	13.40	98.53		
Total lipoids	8.30		2.06		13.60		6.21	

is questionable. As has been mentioned, the values found by various investigators for the lipoid constituents of normal skin vary greatly. If these figures are compared with those given by Montgomery and Osterberg, it would appear that in 3 cases (that of Usher and Rabinowitch, that of Zeisler and Caro and 1 of ours) the values for total lipoids were high, for Montgomery and Osterberg concluded that the total tissue lipoids should represent, on the average, less than 3 per cent of the total wet weight of the specimen examined. Figures given by Usher and Rabinowitch on a section of normal skin from the same patient whose necrobiotic lesions they studied chemically are in close agreement with those given as normal by Montgomery and Osterberg. Usher and Rabinowitch found in this normal skin 3.30 per cent of total lipoids, of which the total cholesterol equaled 0.50 per cent (15.1 per cent of the

32 Michelson, H. E., and Laymon, C. W. *Necrobiosis Lipoidica Diabeticorum* (Urbach), *Dermatitis Atrophicans Lipoides Diabetica* (Oppenheim), J. A. M. A. **103** 163-169 (July 21) 1934.

33 Balbi, E. *Ricerche intorno alla patogenesi della necrobiosis lipoidica diabetica Urbach-Oppenheim*, *Gior. ital. di dermat. e sif.* **74** 14-43 (Feb) 1933, abstracted, *Arch. Dermat. & Syph.* **28** 572-573 (Oct) 1933.

total lipoids), the cholesterol esters 0.07 per cent (2.1 per cent of the total lipoids), the free cholesterol 0.45 per cent (13.9 per cent of the total lipoids) and the lecithin 1.50 per cent (45 per cent of the total lipoids). In 3 of these cases, also, the lecithin was higher than normal, especially in our first case and in the case reported by Zeisler and Caro, in which the lecithin represented 155 per cent and 159 per cent, respectively, of the total lipoids. In 2 of the 4 cases the total cholesterol was elevated when compared with the 5 to 15 per cent of the total lipoids given as normal by Montgomery and Osterberg. In our first case it represented 20 per cent of the total lipoids, in the case reported by Usher and Rabinowitch, 26.5 per cent of the total lipoids. In our case most of the cholesterol was in the combined form, which is the reverse of what was found in the case reported by Usher and Rabinowitch.

The values for fatty acids were determined only in our cases. In our second case these were markedly elevated, representing 98.5 per cent of the total lipoids, of which only 8.09 per cent was in the form of lecithin. In this case we suspected but were not able to prove that not all of the subcutaneous fat was trimmed off prior to analysis, so that an excessive amount of neutral fats may have been included.

The pathogenesis of this condition, therefore, remains obscure. Because of the high incidence of vascular changes seen in the lesions of necrobiosis lipoidica, many authors have assumed that this disease is essentially due to damage to the small blood vessels of the corium, possibly by circulating toxins, with subsequent thrombosis, necrosis and secondary imbibition of fat particles. Reasoning along this line, one might suppose that if vascular injury plays a prominent role in the development of the cutaneous lesions, evidence of vascular damage at other sites should be found in the majority of cases. As has been mentioned, Boldt found a high percentage of instances of vasomotor instability and many instances of hypertension. However, in only 3 or 4 of the cases encountered elsewhere were the vessels of the extremities reported as sclerotic, and in only a few were changes in the retinal vessels reported. In our series, only 1 patient had any degree of sclerosis of the peripheral vessels, although in 3 changes in the retinal vessels were found. In the 1 case in which peripheral sclerosis occurred, this was of such a degree that amputation of one leg was necessary. Microscopic studies of the vessels in this case showed intimal proliferation and deposition of fatty particles in the regions of proliferation. However, these changes in the patient, a 60 year old woman, may have been entirely related to her age, because elderly patients who have arteriosclerosis present essentially these same pictures. Indeed, the vessels of two lower extremities removed from 2 elderly patients who had diabetes mellitus and who did not have necrobiosis were studied here, and there was found practically the same histologic picture as that observed in

the case in which necrobiosis was present. It should also be pointed out in this connection that many diabetic patients have changes in both the retinal and the peripheral vessels of as great a degree as was shown by any of the patients who had necrobiosis, although they had not yet experienced the development of cutaneous lesions. However, failure to find generalized arteriosclerosis in any considerable number of cases of necrobiosis cannot be considered as absolute evidence against the hypothesis of primary vascular damage as a background for these lesions, because localized arteriolar damage (in the skin, for example) has been known to occur in the absence of generalized vascular changes.

The other hypothesis which has been considered is that the cutaneous lesions are secondary to changes in the general metabolism of fat. However, as has already been pointed out, the blood lipoids have not been found to be constantly altered, and the significance of the changes found in the tissue lipoids is questionable. Furthermore, there is no reason to assume that there has been any alteration in the metabolism of fat of the 8 patients who did not have diabetes mellitus, although in the only cases in which any studies of the blood lipoids were made the results are at variance with each other. In the cases reported by Goldsmith only a determination of cholesterol was made, and the value, 150 mg per hundred cubic centimeters, was within normal limits. In 3 cases in which diabetes was not present, reported by Boldt, the value for blood cholesterol was more than 200 mg, 239 mg and 233 mg per hundred cubic centimeters respectively. In 3 of his cases, also, the values for fatty acids were somewhat elevated (485 mg, 400 mg and 614 mg per hundred cubic centimeters). It should be pointed out, too, that the presence of diabetes mellitus itself in these cases of necrobiosis occurring in association with the former disease may have been responsible for any alteration found in the blood lipoids.

TREATMENT

Treatment, either local or general, for those patients who have diabetes mellitus has been of little avail in the majority of cases in which necrobiotic lesions are present. These lesions typically run an indolent, chronic course, either slowly enlarging over a period of months or years or slowly receding to form depressed scars. Control of the glycosuria with proper diet and insulin seems to have little effect on them, although some authors (Feldman, Klaber³⁴, Kren³⁵) have reported good results with diets low in fat. Three of the patients at the

34 Klaber, R. Necrobiosis Lipoidica Diabeticorum (Urbach-Oppenheim), *Proc Roy Soc Med* **27** 713-714, 1934.

35 Kren. Necrobiosis lipoidica diabeticorum, *Zentralbl f Haut- u Geschlechtskr* **49** 580, 1934-1935, **55** 186 and 614-615, 1936-1937, **58** 2-3, 1938.

clinic were placed on this type of diet, but no improvement occurred in the period of observation (several months to a year)

Local treatments have been of a wide variety. Several authors (Urbach, Zeisler and Caro) have tried injection of insulin at the site of the lesions. In no instance has this treatment resulted in healing of the lesions. Ultraviolet light therapy, irradiation and various local medications have been equally unsuccessful in accelerating healing of these lesions.

REPORT OF CASES

CASE 1—A white American woman aged 31 was first seen at the clinic in June 1936. She related a long family history of diabetes mellitus in both her mother's and her father's families. The patient had one sister, who was living and who had diabetes. The patient had classic symptoms of diabetes for the first time in 1926, at that time she was given a weighed diet. Twelve units of unmodified insulin was administered morning and evening. Shortly thereafter the diet was changed to a qualitative one, which she had followed since that time. Control of the disease had been poor. She rarely tested her own urine and in 1935 was in coma. In 1927 or 1928 an erythematous plaque-like scaling eruption developed on the dorsa of both feet. She thought that this had appeared at sites of irritation caused by her shoes. Shortly after this eruption appeared, a similar lesion developed on the anterior tibial surface of the right leg, just below the knee. The lesions were not itching or weeping but gradually spread at their peripheries. A variety of local treatments, including use of ultraviolet light, had been tried, without relief.

General physical examination gave essentially negative results. The concentration of hemoglobin and the numbers of erythrocytes and leukocytes were within normal limits, blood flocculation tests gave negative results, and the basal metabolic rate was -14 per cent.

On examination of the skin, regions of glazed, dry, scaling skin were found on the dorsa of both feet and on the right anterior tibial surface. A diagnosis of *necriobiosis lipoidica diabeticorum* was made on the clinical appearance alone, because the patient refused a biopsy.

Grossly, the vessels of the extremities were open, and the capillaries were normal. Funduscopic examination, however, revealed numerous scattered large and small punctate hemorrhages in the retina with relatively few exudates of the central punctate diabetic type, but cotton-wool exudates were present in a number of places. The veins of the retina were full and the arteries mildly narrowed, but there was no definite sclerosis.

Determination of the values for blood lipoids gave essentially normal results, cholesterol, 200 mg and 241 mg per hundred cubic centimeters on two separate occasions, cholesterol esters, 144 mg per hundred cubic centimeters, lecithin, 245 mg per hundred cubic centimeters, fatty acids, 322 mg per hundred cubic centimeters, and total lipoids, 522 mg, per hundred cubic centimeters.

The value for blood sugar on admission was 280 mg per hundred cubic centimeters, and the urine contained 23.8 Gm of sugar in a twenty-four hour sample, tests for acetone and diacetic acid gave positive results. With a diet of 104 Gm of carbohydrates, 62 Gm of protein and 89 Gm of fat plus 40 units of protamine zinc insulin every morning, the glycosuria rapidly disappeared. The patient was sent home on this regimen.

CASE 2—A Polish woman aged 43 was first seen at the clinic in August 1937. A family history of diabetes mellitus was not obtainable. The cutaneous lesions had developed prior to the onset of diabetes. Four brownish plaques, one on each calf, one on the right ankle and one on the left wrist, developed within one month in 1935 and slowly became enlarged during the next two years. Local treatment was without success, and the patient suffered somewhat from itching and burning of the lesions. However, the diabetes had not been diagnosed before she came to the clinic. At that time the patient had acidosis with a blood sugar level of 349 mg per hundred cubic centimeters and 33.07 Gm of sugar in a twenty-four hour specimen of urine, tests for acetone and diacetic acid gave positive results.

Except for the cutaneous lesions and changes in the eyegrounds, general physical examination gave essentially negative results. On the left wrist, on both calves and on the right ankle were roughly circinate, well defined, smooth, waxy, slightly elevated brownish plaques. These were firm and not tender and showed central scarring and telangiectasia. Biopsy of one lesion showed the typical histologic picture of necrobiosis lipoidica diabetorum.

Fundusoscopic examination showed only an exaggerated light reflex on the part of the retinal arteries, but not actual sclerosis, a few white dots were also present in the retina.

Studies of the blood lipoids revealed essentially normal values throughout, as follows: cholesterol, 248 mg per hundred cubic centimeters on one occasion and 189 mg per hundred cubic centimeters on another, five days later, cholesterol esters, 120 mg per hundred cubic centimeters, lecithin, 227 mg per hundred cubic centimeters, fatty acids, 402 mg per hundred cubic centimeters on admission and 303 mg per hundred cubic centimeters five days later, total lipoids, 650 mg per hundred cubic centimeters on admission and 492 mg per hundred cubic centimeters five days later.

The glycosuria was readily controlled by a weighed diet and by the administration of 30 units of protamine zinc insulin and 25 units of crystalline (Lilly) insulin every morning, but during her stay at the clinic (ten days), change in the cutaneous lesions was not observed.

CASE 3—A white Canadian woman aged 29 was first seen at the clinic in June 1938. She did not give a family history of diabetes. The cutaneous lesions had developed about four months after the first appearance of the symptoms of diabetes mellitus, although the latter was not diagnosed until about seven months after that time. In May 1935 malaise and weakness first developed, the condition was diagnosed as adenoma of the thyroid without hyperthyroidism. Urinalysis at that time gave normal results.

In November the patient became pregnant. She did not gain weight during the pregnancy, but in January 1936 she actually began to lose weight, mild polyuria, polydipsia, polyphagia and pruritus vulvae developed. However, then, as throughout her pregnancy, urinalysis at intervals were reported as giving negative results.

In April, firm, yellowish subcutaneous plaques appeared on the dorsa of the feet and gradually increased in size. These were never painful and never ulcerated. In July the patient bruised her left leg (on the lower part of the anterior tibial surface), and a similar plaque appeared at the site of the injury. About the same time she gave birth at term to a stillborn child. It is of interest to note that during the last trimester of pregnancy the symptoms of diabetes practically disappeared and that they did not recur to any marked degree after delivery. It was not until just after a thyroidectomy, in November, that glycosuria was discovered.

She was given a weighed diet, and 10 units of unmodified insulin was administered every morning and evening. The patient's attitude toward her condition was one of indifference, she rarely tested her own urine. The cutaneous lesions did not increase or decrease in size after the institution of insulin therapy. In June 1937, 30 units of protamine zinc insulin was given every morning.

The findings on general physical examination were essentially normal. The concentration of hemoglobin and the numbers of erythrocytes and leukocytes were normal, blood flocculation was normal, and the basal metabolic rate was $+9$ per cent. The results of fundusoscopic examination were negative, and the vessels of the extremities were open. Examination of the skin revealed on the dorsa of the feet and on the anterior tibial surface of the left leg elevated, firm, well defined yellow-centered plaques which had reddish brown borders and a fine plexus of veins on the surface. The patient refused a biopsy.

In this case also the values for the blood lipids were entirely within normal limits, cholesterol, 187 mg, cholesterol esters, 132 mg, lecithin, 212 mg, fatty acids, 361 mg, and total lipoids, 548 mg, per hundred cubic centimeters.

The patient was sent home after being instructed to take a diet free of animal fat and with a low content of phosphorus plus 20 units of protamine zinc insulin and 10 units of Lilly crystalline insulin every morning. Several months later she reported no improvement in the lesions.

CASE 4—A white American woman aged 27 was first seen at the clinic in August 1938. She did not give a family history of diabetes. The patient had diabetes which dated back to 1929, at that time the classic symptoms of diabetes suddenly developed, and glycosuria was found. She was given a weighed diet, and 50 units of unmodified insulin was administered twice daily. She followed this program for one year, then changed to a qualitative diet, 20 units of unmodified insulin being administered three times daily. On this regimen control of the disease was very irregular. She had frequent insulin reactions and was in a state of diabetic coma twice.

In 1932 several small reddish regions appeared on the anterior tibial surfaces of the legs and on the dorsa of the feet. Each of these lesions ran an asymptomatic course of about six weeks. During the first half of this period the lesions increased gradually and slightly in size, then gradually receded, leaving depressed scars. During the next six years several such lesions at the same sites appeared and went through the same cycle. Two or three months prior to her registration at the clinic one of these lesions developed over the external malleolus of the left ankle and gradually increased in size.

Physical examination revealed in addition to the cutaneous lesions (1) bilateral cystic mastitis, (2) an apical systolic murmur and (3) a retroverted uterus with prolapse of the adnexa. The blood was normal, and blood flocculation was normal. Roentgen examination of the thorax gave negative results. Fundusoscopic examination revealed nothing of importance, and the vessels of the extremities were open. Examination of the skin showed a brownish plaque just above the left external malleolus plus several depressed scars over the anterior tibial surfaces. The patient refused a biopsy.

In this case, also, the values for blood lipids were normal, being estimated as follows: cholesterol, 203 mg, cholesterol esters, 132 mg, lecithin, 227 mg, fatty acids, 295 mg, and total lipoids, 498 mg, per hundred cubic centimeters.

The patient responded well to a diet (basal plus 50 per cent) and was sent home with instructions to use 30 units of protamine zinc insulin and 10 units of crystalline insulin every morning plus 10 units of crystalline insulin every evening.

CASE 5—A white American girl aged 14 years was first seen at the clinic in October 1928, at the age of 5 years. She complained of lifelong enuresis and of failure to gain weight. Glycosuria had been observed elsewhere one week prior to her registration at the clinic, and she had been given a qualitative diet.

Physical examination at that time disclosed no evidence of active infection in the upper portion of the respiratory tract, roentgen examination of the thorax gave negative results, although the patient had been having frequent colds. The urine was free of sugar, but the value for blood sugar was 200 mg per hundred

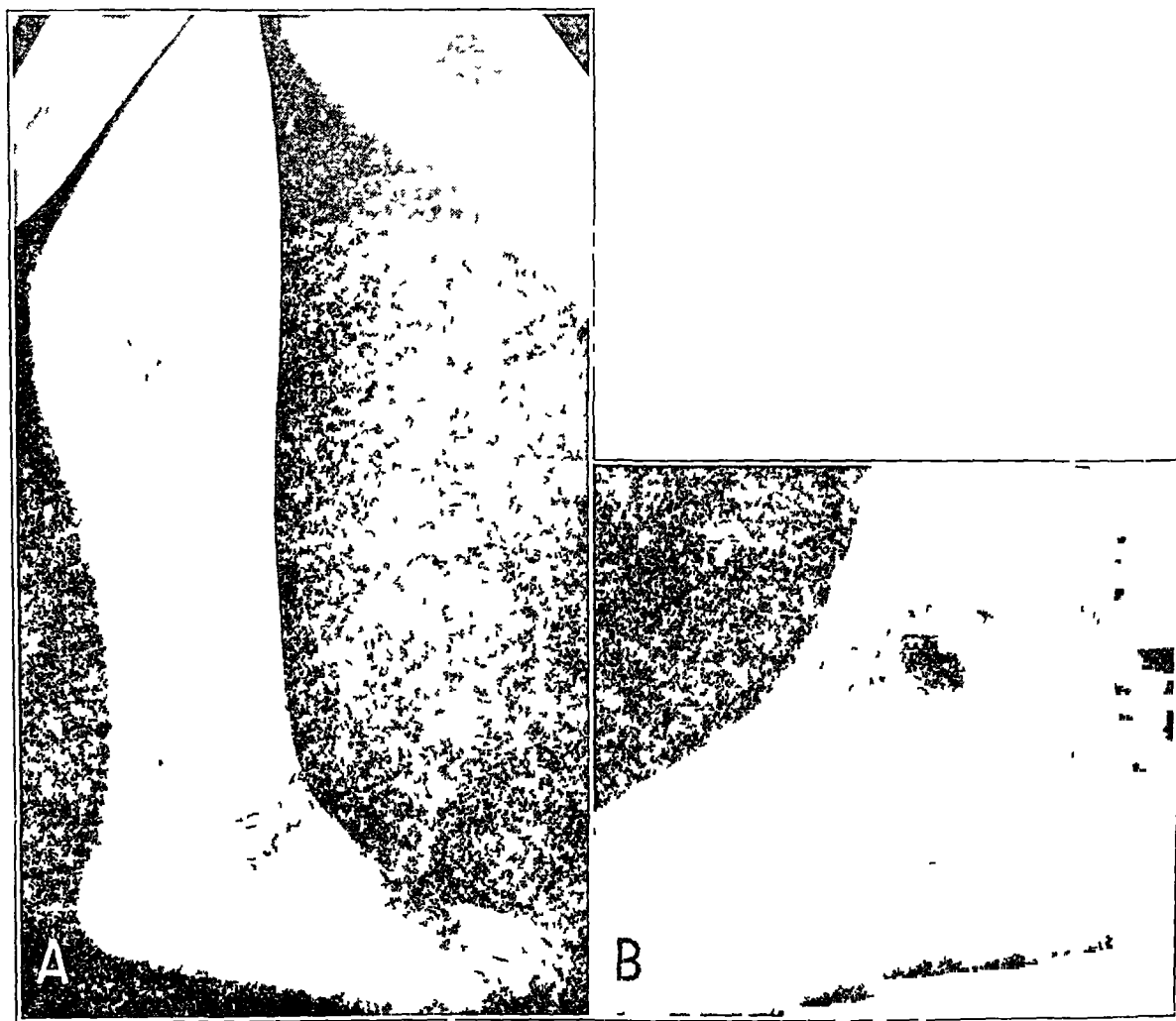


Fig 1—A, necrobiosis lipoidica diabetorum, with multicolored hypertrophic and atrophic scaling plaques. B, necrobiosis lipoidica diabetorum. Note the large plaque which is yellow with reddish blue borders and central ulceration.

cubic centimeters on admission. The blood was normal, and flocculation tests gave negative results. Study of the blood lipoids was not made at that time. The girl was sent home after being instructed as to a weighed diet and was directed to take 2 units of unmodified insulin twice daily.

She gradually increased the diet and the dose of insulin over the next nine years until she was taking 25 units of the unmodified insulin twice daily. For two years prior to her second registration at the clinic, in 1938, she had been

receiving 50 units of protamine zinc insulin every morning. Her cooperation as regards diet was poor, however, and in 1934 she was in diabetic coma for several hours. Together with the poorly controlled diabetes, there had been delayed puberty, she had never menstruated up to the time when she was seen in 1938.

The first cutaneous lesion appeared on the lower part of the left leg in 1930. It was a yellowish plaque which ulcerated soon after its development and then slowly healed within a month. The patient had no further cutaneous lesions until 1936, when plaques similar to the first began developing, one after the other, on the lower parts of both legs and on the anterior surface of the right thigh.

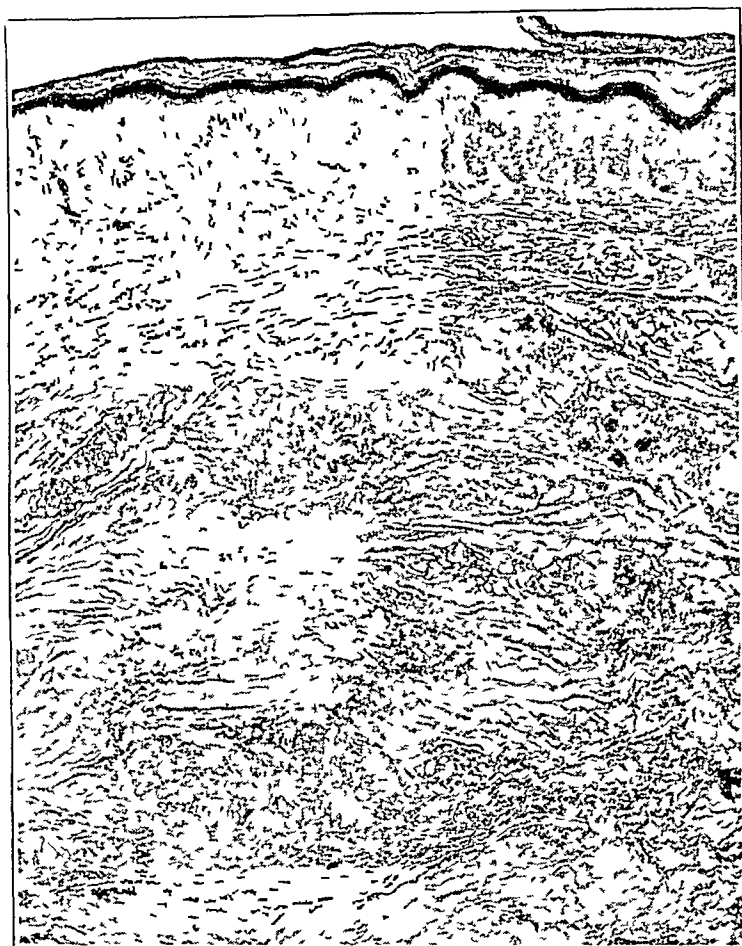


Fig 2—Necrobiosis lipoidica diabeticorum. A region of pseudonecrosis is present in the cutis, surrounded by extracellular deposits of lipoids that appear as black granules. A mild inflammatory reaction is present, as is evident by infiltration of lymphocytes and leukocytes around the regions of necrosis. Sudan III stain.

Several weeks prior to her second registration, an ulcerated lesion developed on the lateral surface of the left ankle, which persisted (fig 1).

On physical examination at the time of her registration the patient was poorly developed but in good general health otherwise. The blood was normal, blood flocculation gave negative results and roentgen examination of the thorax gave negative results. Funduscopic examination also gave negative results, and the vessels of the extremities were open.

Examination of the skin showed (1) on the lateral aspects of the left ankle a large punched-out ulcer, surrounded by a raised, rolled border, (2) on the lateral

aspect of the right ankle a large erythematous, scaling lesion, and (3) on the lower portion of both legs and on the anterior surface of the right thigh a few infiltrated, dense plaques of definite yellowish hue, crossed superficially by delicate blood vessels. The mucosa of both the soft palate and the eyelids had a definite yellowish hue. Biopsy of the yellowish plaques showed the typical histologic picture of necrobiosis lipoidica diabetorum (fig 2).

Quantitative determinations of the lipid constituents of both the blood and the cutaneous lesions were made. As has already been pointed out, the value for tissue lecithin was high in this case. None of the values for blood lipids were markedly elevated, although the fatty acids and the total lipids were sufficiently greater than normal to make them worthy of note, 500 mg and 728 mg per hundred cubic centimeters respectively. The value for blood cholesterol was 228 mg, that for cholesterol esters 177 mg, and that for lecithin 250 mg, per hundred cubic centimeters.

The patient was sent home after receiving instruction as to a weighed diet of relatively low animal fat content and was directed to use 60 units of protamine zinc insulin and 45 units of crystalline insulin every morning. When last heard from, in September, she reported that the lesions were about the same as they had been in June.

CASE 6—A white American woman aged 61 was first seen at the clinic in November 1938. A family history of diabetes was not elicited. She stated that she had repeatedly had lesions on the lower portion of both legs, which occurred singly or in crops, as reddish papules, during the preceding two or three years. Each of these lesions persisted for three or four weeks, during which time they first increased a little in size and then gradually faded, to leave depressed scars covered with fine scales. A salve had been used in treatment at home. The lesions were never painful and never became ulcerated. During May and June she was incapacitated with two slowly healing, somewhat painful ulcers on the left foot. Under treatment with a salve and a pressure bandage these lesions finally cleared up, and depressed scars remained. Because the patient failed to regain strength after this time, a urinalysis was finally done, in August, and glycosuria was discovered. She had had none of the classic symptoms of diabetes mellitus. She was given a weighed diet, and 30 units of protamine zinc insulin was taken every morning, a program which only she, of all our patients, carefully followed. She also had been taking compound solution of iodine U S P, 10 to 15 drops three times a day, since August, because at that time a basal metabolic rate of +44 per cent had been discovered.

In September the patient first began having pains in both calves, and in October she again had ulcerated lesions on the left foot and leg. At about the same time she began to notice numbness, burning and tingling of the legs. A wide variety of local treatments for the ulcer failed to relieve the pain and did not cause healing of the ulcers.

On admission a small thyroid adenoma was present, but tremor or other evidence of hyperthyroidism was not found, except for a basal metabolic rate of +30 per cent. Treatment with compound solution of iodine was not continued, however. The blood was normal, and blood flocculation gave negative results.

Examination of the vessels of the extremities revealed no pulsations and no oscillometric deviations below the knees on either side. Roentgen studies of the lower extremities showed slight calcification in the proximal vessels of the left foot. Narrowing of the retinal vessels, grade 1 (on a basis of 1 to 4) was present, and sclerosis grade 1 (of the chronic hypertensive type) was noted, plus several small

punctate hemorrhages of the diabetic type around the left macular region. The right retina was slightly detached in the temporal zone.

Examination of the skin revealed an ulcerated lesion between the fourth and fifth toes of the left foot, similar to the superficial pyoderma sometimes found in association with diabetes. Cultures of material from this ulcer on the ordinary mediums yielded gram-positive cocci. There was also an ulcerated region measuring 1 by 2 cm, covered with a small black scab, on the medial side of the dorsum of the left foot. This was diagnosed as necrobiosis lipoidica diabetorum.

Two studies of the blood lipoids were made, two days apart. Neither revealed any significant changes. The first showed the value for cholesterol to be 238 mg, that for cholesterol esters 155 mg, that for lecithin 230 mg, that for fatty acids 350 mg and that for total lipoids 585 mg per hundred cubic centimeters. The second showed the value for cholesterol to be 222 mg, that for fatty acids 314 mg, and that for total lipoids, 536 mg, per hundred cubic centimeters.

Despite control of the glycosuria by means of a weighed diet and a proper amount of insulin, excruciating pain in the left leg and foot continued unabated. Local application of 2 per cent procaine and nupercaine ointment to the lesion between the toes of the left foot gave no relief from the pain, nor did either lesion show any tendency toward healing. After ten days of rest in bed and potassium permanganate soaks to the foot, when redness and swelling of the dorsum of the foot appeared, amputation of the left leg just below the knee was performed. A prophylactic dose of combined gas gangrene and tetanus antitoxin was given preoperatively. On the second postoperative day acidosis reappeared, and examination of the stump showed crepitation, which rapidly extended proximally. Amputation at the mid thigh was immediately performed, and postoperatively several doses of the combined antitoxin (more than 100,000 units) were given. These had to be accompanied by histamine administered subcutaneously because of a severe asthmatic reaction to the first dose of the serum. Increased doses of both protamine and crystalline insulin served to control the acidosis within twenty-four hours after it had begun. However, toxicity progressed, and the patient died on the fifth postoperative day.

Microscopic studies were made not only of the necrobiotic lesions on the amputated leg but of the arteries and long nerves. The lesion itself was one of necrobiosis lipoidica. The vessels stained with both hematoxylin and eosin, and fat stains (sudan III) showed intimal proliferation. In the regions of proliferation fat particles were present. Weigert stains of the nerves showed degeneration. It will be remembered that this patient had suffered from extreme pain in that leg. This, as microscopic studies showed, might have been on the basis of poor circulation or neuritis.

CASE 7—An American woman aged 52 was first seen at the clinic in November 1938. She did not give a family history of diabetes. Classic symptoms of diabetes mellitus had developed in 1936, but it was not until 1937 that she was given a qualitative diet and was instructed to take 25 units of unmodified insulin every morning and evening. Control of the disease had been very irregular, and since August she had experienced symptoms of acidosis, including abdominal pains, nausea, vomiting and malaise on repeated occasions. She had lost 50 pounds (23 Kg) since then. Almost since the onset of the diabetes she had noticed repeatedly a single papular lesion on the lower portion of each leg, each of which appeared and faded within one or two weeks. The latest one had developed on the left anterior tibial surface three weeks prior to registration at the clinic, and this lesion had become ulcerated.

Physical examination revealed evidence of acidosis, including acetone breath, air hunger, hot, dry skin, glycosuria grade 4 (on the basis of 1 to 4), acetone and diacetic acid in the urine and a blood sugar level of 338 mg per hundred cubic centimeters, a thin vaginal discharge, which she had had for one year, ready bleeding of the cervix on examination, and an aortic systolic murmur and thrill, although roentgenoscopic examination failed to reveal calcification of the aortic valve. The blood was normal, and the Wassermann reaction of the blood was negative, although both the Kline and the Kahn tests gave positive results. Dilatation, curettage and cervical biopsy revealed no malignant disease. Roentgenoscopic examination of the thorax gave negative results, and the vessels of the extremities were open. Examination of the skin showed a crusted, well circumscribed lesion, 1 by 2 cm, on the lateral surface of the left ankle. Clinically this was considered necrobiosis lipoidica diabetorum, although a biopsy was not performed. All the values for blood lipoids were low, ranging as follows: cholesterol, 137 mg, cholesterol esters, 87 mg, lecithin, 192 mg, fatty acids, 270 mg, and total lipoids, 401 mg, per hundred cubic centimeters.

The glycosuria rapidly cleared after a weighed diet was prescribed in addition to a combination of protamine zinc and crystalline insulin, but the lesions failed to change in the two weeks during which the patient was hospitalized here.

CASE 8—A white American man aged 27 was first seen at the clinic in August 1939. He did not give a family history of diabetes. Classic symptoms of diabetes mellitus had developed in 1935. At that time the concentration of blood sugar was 375 mg per hundred cubic centimeters. He was given a quantitative diet and 30 to 40 units of unmodified insulin daily. One year later he began a qualitative type of diet which he had followed since that time. Also, in the last year, he had been using 30 units of protamine zinc insulin plus 10 units of unmodified insulin daily instead of the unmodified insulin alone. On the whole, his control of the disease had been poor. He tested his urine only once a week, and then it was always "heavy with sugar." The concentration of blood sugar varied from 180 to 375 mg per hundred cubic centimeters. However he had never been in coma and had not experienced insulin reactions. For one and a half years he had had some pains in both legs plus burning and tingling in the feet.

In 1936 a small area of redness appeared on the right shin and gradually became enlarged. Similar lesions appeared around this first one, and as they all became enlarged they coalesced to form a slowly enlarging, red, dry, scaling irregular plaque over the right anterior tibial region. In 1938 a similar lesion appeared on the left calf, and six months later one appeared on the left tibial region. The last-mentioned lesion progressed rapidly. The lesions were tender, especially at their borders. The patient had had various types of treatment for the cutaneous lesions, including eight treatments with roentgen rays to the lesion on the right leg and one treatment with roentgen rays to the lesion on the left leg. General physical examination gave essentially negative results. The concentration of hemoglobin was normal, and the blood flocculation test gave negative results. Examination of the vessels of the extremities revealed nothing significant. The patient did not remain long enough to permit a fundusoscopic examination. Examination of the skin showed on the anterior surface of the lower part of the right leg an irregular, slightly raised reddish plaque with an advancing telangiectatic border and a dry, scaling center which was slightly depressed, the lesion measured 8 inches (20 cm). Biopsy of this lesion showed the typical histopathologic picture. Similar lesions were present on the lower part of the left leg and on the left calf.

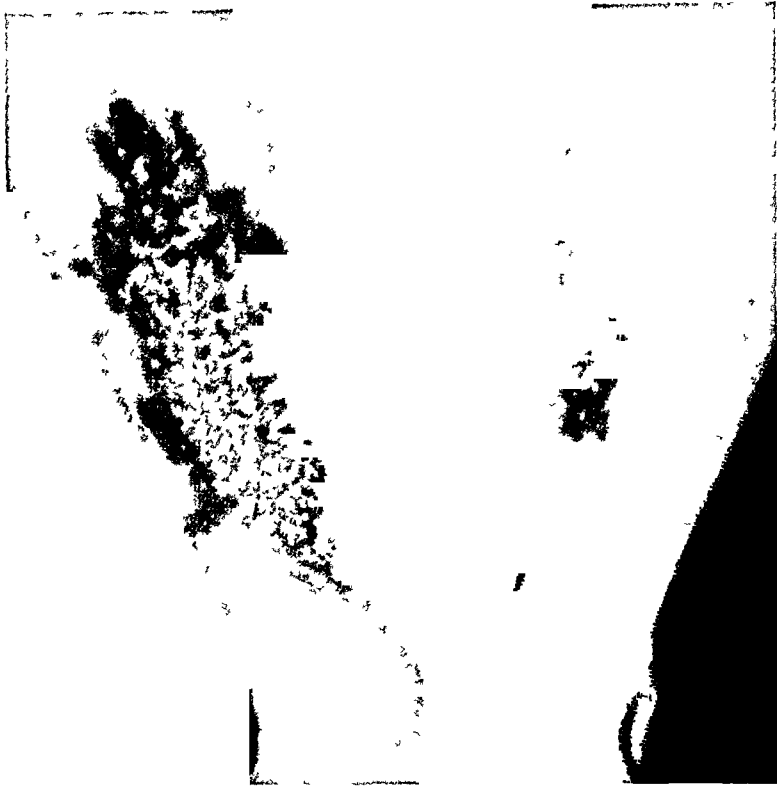


Fig 3—Typical appearance of the lesions of necrobiosis lipoidica diabetorum
Note the multiplicity of colors and the yellowish red center

The values for blood lipoids were entirely within normal limits, being estimated as follows: cholesterol, 208 mg, cholesterol esters, 118 mg, lecithin, 171 mg, fatty acids, 269 mg, and total lipoids, 477 mg, per hundred cubic centimeters. The value for blood sugar on admission was 323 mg per hundred cubic centimeters. Analysis of the necrobiotic lesions quantitatively revealed the figures already given, namely, cholesterol, 0.3 per cent, cholesterol esters, 0.2 per cent, lecithin, 1.1 per cent, total fatty acids, 13.4 per cent, and total lipoids, 13.6 per cent, of the wet weight of the specimen. We have obtained a colored photograph of the lesions in this case (fig. 3).

SUMMARY

Seventy-eight cases of necrobiosis lipoidica diabetorum which have been described in the literature since the first report of this dermatosis by Oppenheim, in 1929, are reviewed. Observations on 8 cases of necrobiosis lipoidica diabetorum encountered at the Mayo Clinic since 1936 are related. More than 87 per cent of all the patients, both those seen elsewhere and those seen at the clinic, had diabetes mellitus, and in 8 typical cases of necrobiosis evidence of diabetes mellitus was not found. In the majority of the cases in the entire series the cutaneous lesions had developed several months to as long as seventeen years after the onset of diabetes, although in about 18 per cent of the cases encountered elsewhere and 25 per cent of those encountered at the clinic the reverse was true, the cutaneous lesions preceding the onset of the diabetes by as long as eight years. All patients were white, and more than 80 per cent were women. The commonest age of onset among all patients was between 10 and 40 years. In those who had diabetes mellitus, the constitutional disease in most instances could be called moderately severe to severe, and in most of them the diabetes had been poorly controlled. Trauma apparently played a definite role in the development of the cutaneous lesions in several cases.

The lesions in this condition are most often reddish papules or yellowish plaques with well defined reddish brown borders, much infiltration and central telangiectasia. They usually occur on the lower parts of the legs. Microscopically the lesions are characterized by changes in the deep layers of the cutis, consisting of necrobiotic regions in which there are granular degeneration of the collagen fibers, loss of elastic fibers and extracellular deposition of various lipoids, surrounded by a region in which the arterioles show intimal proliferation and perivascular monocyctic infiltration. The absence of xanthoma or foam cells containing cholesterol and cholesterol esters differentiates these lesions from those of the other xanthomatoses except lipid proteinosis, which represents a different clinical picture. Quantitative determinations of the lipid constituents of these lesions were suggestive of a relative increase of lecithin in the tissues.

Studies of the blood lipoids have shown that in the majority of all cases encountered elsewhere and in all of the cases encountered at the

clinic the values lay within normal limits. The lesions tended to run a chronic course, and neither local therapy nor, in the case of diabetics, general management tended to speed their healing. In some cases the lesions slowly receded and left depressed scars.

Two ideas regarding the pathogenesis of this condition have been considered: (1) that which assumes the occurrence of a primary vascular injury, possibly by circulating toxins, with secondary thrombosis, necrosis, and fat imbibition and (2) that which assumes a local lipoid disturbance in the skin, based on a general disturbance in fat metabolism. Neither hypothesis has proved satisfactory in the light of studies made both here and elsewhere. Therefore, the pathogenesis of this condition remains obscure.

BANTI SYNDROME (FIBROCONGESTIVE SPLENOMEGALY)

DEFINITION, CLASSIFICATION AND PATHOGENESIS

PAOLO RAVENNA, M D

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The Banti syndrome is still an unsolved problem. The question of cardinal importance is whether the splenomegaly is primary or secondary to portal or hepatic changes.

Banti¹ stated the belief that the trouble lay primarily in the spleen and that the portal and hepatic changes were dependent on the splenic ones. The idea that the splenomegaly was the consequence of circulatory disturbances was put forward by Dock and Warthin² and further developed with the description of the thrombophlebitic splenomegaly³. This theory occupied a position of definite advantage when it was recognized that the structure of Banti splenomegaly was chiefly congestive⁴ and that

1 Banti, G. La splenomegalia con cirrosi epatica, *Sperimentale* (sez. biol.) **48** 407, 1894, La splenomegalie avec cirrhose du foie, *Semaine med.* **14** 318, 1894, Ueber Morbus Banti, *Folia haemat.* **10** 33, 1910.

2 Dock, G., and Warthin, A. S. A Clinical and Pathological Study of Two Cases of Splenic Anaemia, with Early and Late Stages of Cirrhosis, *Am. J. M. Sc.* **127** 24, 1904.

3 (a) Cauchois, A. Splenomegalies chroniques d'origine pylethrombosique, Thesis, Paris, no. 422, Paris, G. Steinheil, 1908. (b) Deve, F. Splenomegalie chronique avec anemie d'origine pylethrombosique, *Normandie med.* **23** 109 (March) 1908. (c) Warthin, A. S. The Relation of Thrombophlebitis of the Portal and Splenic Veins to Splenic Anaemia and Banti's Disease, *Internat. Clin.* **4** 189, 1910. (d) Eppinger, H. *Hepato-lienale Erkrankungen*, Berlin, Julius Springer, 1920. (e) Frugoni, C. La splenomegalia tromboflebitica primitiva, *Arch. di pat. e clin. med.* **3** 574 (Dec.) 1924, La splenomegalie thrombophlebitique, *Rev. belge sc. med.* **10** 227 (April) 1938. (f) Ceconi, A. La splenomegalia tromboflebitica, *Gazz. d. osp.* **50** 265 (March 3) 1929. (g) Klemperei, P. Cavernomatous Transformation of the Portal Vein, *Arch. Path.* **6** 353 (Sept.) 1928.

4 (a) Greppi, E. Il tumore di milza contrattile emorragiparo come probabile forma di splenoangiopatia primitiva, *Minerva med.* **2** 644 (Sept. 22) 1928, Die contractile Milztumor und seine Beziehungen zur thrombophlebitischen Splenomegalie, *Verhandl. d. deutsch. Gesellsch. f. inn. Med.* **40** 615, 1928. (b) Villa, L. Il significato semiologico della contrazione di volume della milza mediante adrenalina per la diagnosi delle splenomegalie voluminose, *Boll. d. soc. med.-chir., Pavia* **3** 479, 1928, Cuore e circolaz. **12** 465, 1928. (c) Larrabee, R. C. Chronic Congestive Splenomegaly and Its Relationship to Banti's Disease, *Am. J. M. Sc.* **188** 745 (Dec.) 1934. (d) Rousselot, L. M. The Role of Congestion (Portal Hypertension) in So-Called Banti's Syndrome, *J. A. M. A.* **107** 1788 (Nov. 28) 1936.

the pressure in the splenic vein was highly increased⁵ But these same signs of portal hypertension were found to be present when an obstructive factor was missing This fact was responsible for the widest gap in the support of the theory of venous congestion as the causative agent and formed an apparent paradox of great interest⁶

It is my opinion, however, that this apparent contradiction may be explained if the portal congestion is considered to be the effect of an increased flow of blood into the spleen ("primary acute congestion") In 1936 I published a detailed study⁷ in which I suggested this interpretation I believe that some important recent contributions by other observers and my successive experience have brought further evidence to the support of this view

The object of this paper is to correlate these various arguments, thus bringing up to date an idea which may have some bearing both on the understanding of the physiology of the spleen and on the clinical management of its circulatory dysfunctions Before proceeding, it seems advisable to suggest a definition and a scheme of classification of the Banti splenomegalies, these preliminary considerations should be constantly borne in mind, as they form the premises of any discussion on the pathogenesis of the syndrome

DEFINITION

Banti's conception of a symptom complex which is dominated by chronic splenomegaly, characterized by certain particular anatomico-histologic changes, due to an unknown agent and recognizable as a separate, clearcut disease can no longer be maintained Many conditions presenting the clinical and pathologic features described by Banti have been shown to be dependent on various known causative agents⁸ The term "Banti's disease" has thus been discarded and "the Banti syndrome" used in its place, though even recently an author,^{8'} with

5 Thompson, W P , Caughey, J L , Whipple, A O , and Rousselot, L M Splenic Vein Pressure in Congestive Splenomegaly (Banti's Syndrome), *J Clin Investigation* **16** 571 (July) 1937

6 (a) Whipple, A O The Combined Spleen Clinic, Surg, Gynec & Obst **64** 296 (Feb) 1937, (b) The Medico-Surgical Splenopathies Introduction, *Bull New York Acad Med* **15** 174 (March) 1939 (c) Rousselot, L M Congestive Splenomegaly, *ibid* **15** 188 (March) 1939

7 Ravenna, P La splenomegalia fibroso-congestizia primitiva con cirrosi epatica e la sua sistemazione fra le sindromi bantiane, *Minerva med* **1** 225 (March 10), 255 (March 17), 276 (March 24), 306 (March 31) 1936

8 (a) Micheli, F Contributo clinico ed anatomopatologico allo studio della varieta luetica del morbo di Banti, *Soc ital per il progr delle sc* **7** 962, 1913 (b) Durr, R Bantimilz und hepatolienale Fibrose, *Beitr z path Anat u z allg Path* **74** 418, 1924

8' Patrassi, G Il morbo di Banti inteso come cirrosi splenomegalica a decorso protratto, *Arch per le sc med* **69** 259 (April) 1940

remarkable lack of criticism, insisted on the term Banti's disease, in spite of the fact that he admitted the multiple etiologic considerations. Even the idea of a Banti syndrome has been the object of repeated criticisms until recently.

It must be granted, however, that chronic splenomegalies not related to any typical disease of the blood, to intrasplenic deposits of lipoids or to tumors are a matter of universal experience, though their existence has been noted more often in certain countries than in others. Banti⁹ and several other Italian authors⁹ emphasized that this type of splenic enlargement is more or less frequently associated with hepatic cirrhosis. As to the relation between splenomegaly and cirrhosis, it was noted that the same degrees of splenic enlargement are found without any lesion of the liver, or with diverse stages of typical cirrhosis. There was enough evidence, it was believed, to warrant the assumption that this splenomegaly is either autonomous or coordinated with, but not dependent on, the hepatic lesion.

This intimate relation between splenomegaly and cirrhosis of the liver, in which the splenic enlargement constitutes, apparently at least, the primary lesion, forms the basis of the modern idea of the Banti syndrome¹⁰. To the Banti syndrome can therefore be ascribed the conditions in which the morbid picture is dominated by a considerable chronic splenic enlargement, nonhemolytic anemia and leukopenia. The clinical course is often punctuated by repeated severe hematemeses and sometimes by transitory or permanent ascites. More or less constantly these symptoms are coupled with cirrhosis of the liver. Splenomegalies due to diseases of the blood, to intrasplenic deposit of lipoids or to tumors must not be confounded with Banti syndrome. Splenic anemia, a term which from Griesinger's times up to recent years¹¹ has pooled all these and other various morbid conditions, is really void of any particular meaning¹². Almost all chronic splenomegalies are, in point of fact, associated with such a type of anemia.

9 (a) Micheli, F. Sul morbo di Banti, *Arch per le sc med* **33** 351, 461 and 495, 1909, *Sistemazione e patologia delle splenomegalie primitive*, Turin, Unione tipografica editrice torinese, 1910. (b) de Vecchi, B., and Zanotti, P. Su di una particolare splenomegalia primitiva, *Sperimentale, Arch di biol* **82** 217, 1928.

10 (a) Greppi, E. La maladie de Banti. Evolution et état actuel du problème, *Rev belge sc med* **10** 237 (April) 1938. (b) Ravenna.⁷

11 Hanrahan, E. M. Splenic Anemia. A Study of End Results With and Without Splenectomy Based on Thirty-Five Cases, *Arch Surg* **10** 639 (March) 1925. Mayo, W. J. Certain Blood Dyscrasias Dependent on Pathologic Conditions of the Spleen, *J A M A* **88** 815 (Sept 13) 1924.

12 (a) Naegeli, P. *Blutkrankheiten und Blutdiagnostik*, ed 5, Berlin, Julius Springer, 1931, p 560. (b) Klemperer, P. The Pathologic Anatomy of Splenomegaly, *Am J Clin Path* **6** 99 (March) 1936, The Spleen, in Downey H. *Handbook of Hematology*, New York, Paul B Hoeber, Inc., 1938, vol 3, pp 1591-1728.

CLASSIFICATION

Actual classifications are mainly founded on morphologic bases. Macroscopic and histologic examinations have decided whether the splenomegaly had to be classified as fibrous or fibroadenic,¹ congestive⁴ or siderotic.¹³ Naegeli's¹² and McNee's¹⁴ classifications were based on which tissue was prevalently damaged. The concomitant presence of hepatic cirrhosis or of thrombophlebitis gave rise to other classes (Eppinger^{3a} and Rousselot^{6c}). All these classes do not differentiate nosologic entities but merely point to characteristics and courses which may depend either on the same or on different causative agents.

In syphilitic patients with the Banti syndrome, for instance, all the aforementioned aspects have been recorded (Michel^{8a} and Minot¹⁵), either with or without histologic signs of syphilis (Ravenna⁷). The only correct diagnosis would be that of Banti syndrome of syphilitic origin, which offers a comprehensive definition of the disease and not only one particular aspect.

One of the best schemes for classification was suggested by Klemperei,^{12b} and it was based on pathogenetic criteria. But a lasting classification should be based on the etiology. Only conditions of which the cause is not determined may be divided, somewhat arbitrarily, from the standpoint of morphologic aspects. It would then be correct to make a diagnosis of primary or cryptogenetic splenomegaly with prevailing congestion (hemorrhages or siderosis) or with prevailing fibrosis (fibroadenia or cirrhosis). The latter class evidently includes instances presenting all the etiologic and morphologic characters described by Banti, and it therefore may conserve the name of Banti's disease.

The following scheme may be suitable for a simple classification.

A	Of known origin	{ infective toxic	{ syphilis leishmaniasis schistosomiasis malaria tuberculosis
			{ alcohol lead phosphorus
B	Of undetermined origin (primary fibrocongestive splenomegaly with cirrhosis)	{ with prevailing congestion with prevailing fibrosis (Banti's disease)	

13 Gamna C. Contributo alla conoscenza della splenomegalia primitiva. *Haematologica* 4 129, 1923.

14 McNee, J. W. The Spleen. Its Structure, Function and Diseases, *Lancet* 1 951 (May 2), 1009 (May 9), 1063 (May 16) 1931.

The progress of the general knowledge of etiology will enlarge class A, with the inclusion of other causative agents, while the number of cases ascribed to class B is bound to decrease and ultimately disappear.

CLINICAL AND PATHOLOGIC NOTES

For a long time great importance was attributed to the anemia which almost constantly accompanies Banti's syndrome. It is of moderate degree, normocytic and nonhemolytic and is associated with well marked leukopenia, relative or absolute monocytosis, and frequently with decrease of blood platelets. Its significance decreased considerably when it was generally recognized that this type of anemia, as pointed out by Micheli in 1903,¹⁶ is usually associated with any considerable splenic enlargement, from whatever cause.

Lately attention has been drawn to a condition of splenic and portal congestion of high degree, and it has been noted that, being less considerable or absent in splenomegalies from other causes, this congestion forms a salient and typical feature of Banti splenomegalies. Its presence is inferred from (1) the pronounced decrease of splenic volume after injection of epinephrine¹⁷ or after hemorrhage, (2) the frequent occurrence of copious hemorrhages from the gastrointestinal tract, (3) the frequency of transitory or permanent ascites, and (4) the hypertension in the splenic veins, as determined during surgical intervention.⁵

The spleen is invariably greatly enlarged but shows no specific characteristics, and this fact accounts for the long opposition that Banti's idea met with when morphologic criteria were dominating morbid anatomy as well as clinical diagnostics. A certain similarity of lesions, however, was noted, consisting in connective and elastic hyperplasia of the capsule and trabeculae and fibrosis and hyperplasia of the reticular framework of the splenic pulp. The liver is normal in some instances but mostly presents various degrees of Laennec's cirrhosis. Moreover, careful examination showed many definite signs of portal congestion, represented by (1) the gross and histologic aspect of the spleen—dilatation of the sinuses, intrasplenic hemorrhages and their residuals and the siderotic nodules¹⁸, (2) the dilatation of small vessels inside the spleen,

15 Minot, G. R. Anemias, in Christian, H. A. Oxford Medicine, New York, Oxford University Press, 1932, vol. 2, p. 642.

16 Micheli, F. Note ematologiche sulla malattia di Banti, Riv. di clin. med. **4** 65 (May), 81 (June), 97 (July) 1903.

17 Greppi^{4a} Villa^{4b}

18 B. de Vecchi, B. Picchi and G. Patrassi (Ricerche sistematiche sulla genesi e sul valore delle lesioni spleniche conosciute col nome di aree di Gamna, Arch. di pat. e clin. med. **8** 17 [Jan.] 1929) and C. Oberling (Le rôle pathogène de la mycose splénique de Banti, Presse méd. **36** 2 [Jan. 4] 1928), examining some of Banti's own slides, observed siderotic nodules also in his original cases.

of the splenic veins and its roots and of portal and mesenteric veins,¹⁹ and (3) the dilatation of collateral portal-general paths of circulation. The aforementioned frequency of gastroesophageal hemorrhages and ascites is, of course, a pathologic as well as a clinical sign of portal congestion.

Pathologists usually evaluate the state of congestion from the anatomic aspect of the spleen removed surgically or at necropsy. This criterion is misleading, as the spleen is larger during life than after death and is subject to shrinkage as an effect of various operative procedures, of anesthetics (both ether and chloroform) and of epinephrine, which is often purposely given. A further amount of blood flows out of the splenic tract of resected veins. That is possibly the reason why the presence of congestion had been so long overlooked by pathologists and by Banti himself. But, once recognized, the importance of splenic and portal hypertension was stressed increasingly.²⁰ Some authors²¹ have used the term congestive splenomegaly as synonymous with Banti's syndrome. Piney²² wrote "There seems to be little doubt that Banti's disease is essentially a pathological state of the vascular system of the spleen," and Greppi²³ noted that the vascular factor was becoming the "Leit-motif" of splenic pathology.

Thrombosis of the splenic and portal veins, their cavernomatous transformation and their stenosis by external compression due to various causes or various stages of hepatic cirrhosis were often noted and referred to as possible or probable causes of the splenic and portal congestion. Experimentally, however, attempts to produce chronic splenomegaly by means of varied derangements in the portal or splenic circulation have been uniformly disappointing.^{23a} Only Rousselot and Thomson^{23b} have claimed positive results, obviously, their experiments must be confirmed independently before definite conclusions be drawn.

19 McMichael, J. The Pathology of Hepatosplenic Fibrosis, *J Path & Bact* **39** 481, 1934. Rousselot^{6c}

20 (a) Villa, L. Sulla retrattilità splenica, *Rassegna med* **15** 127 (Sept 30) 1935. (b) McNee, J. W. Croonian Lectures on Liver and Spleen. Their Clinical and Pathological Associations, *Brit M J* **1** 1017 (June 4), 1068 (June 11), 1111 (June 18) 1932. McMichael¹⁹

21 Greppi^{4a} Larrabee^{4c} Rousselot^{4d}

22 Piney, A. Recent Advances in Haematology, ed 4, London, J & A Churchill, Ltd, 1939, p 294.

23 Greppi, E. Morbo di Banti 1938, *Riv di clin med* **40** 52 (Jan) 1939.

23a Castiglioni, G, and Pepere, M. Ricerche sperimentali intese a modificare il circolo splenico, *Arch ital di anat e istol pat* **11** 14 (Dec) 1939.

23b Rousselot, L. M, and Thomson, W. P. Experimental Production of Congestive Splenomegaly, *Proc Soc Exper Biol & Med* **40** 705 (April) 1939.

A fact of the utmost importance for the proper understanding of this vascular condition was the observation that all these clinical and pathologic signs of congestion could also be found in the absence of any obstructive factor in the portal vessels. Such an event was rarely considered in its real significance, though it clearly resulted from the pathologic records of most of the instances of what was described as Banti's disease in the old and modern literature, and McNee^{20b} had already noted that in Banti's disease high portal pressure and changes in the spleen precede the onset of marked fibrotic changes in the liver. Shortly thereafter Klempere^{12b} wrote that chronic portal stasis is not the sole cause of splenic enlargement and that cases have been observed in which the splenomegaly becomes clinically manifest at a period when there is no indication of a hepatic disorder. In other cases, he stated,^{12b} the splenomegaly occurs concomitantly with the hepatic alterations and not subsequently, it is not dependent on or secondary to them. Six recent cases of congestive splenomegaly without peripheral obstacle to the venous return from the spleen were cited by me,⁷ and 2 others have since come to my attention. Two similar instances were referred to by Lariabee^{4c}. Twenty-two others have been collected by Rousselot,^{6c} from a total of 55 cases of congestive splenomegaly under his observation in the spleen clinic of the Presbyterian Hospital of New York. If it were borne in mind that often the obstacle to the venous return from the spleen could not logically have accounted for the splenomegaly (frequently old splenomegalies are associated with slight cirrhosis or with recent thrombosis, as observed by Davies²⁴ and myself⁷), the number of cases of apparently nonsecondary splenomegaly would increase considerably.

Also the observations in cases of schistosomal splenomegaly are rather against the idea of ascribing the splenomegaly to the local deposition of ova and the subsequent fibrosis or to the thrombosis of large portal veins, which is extremely rare in this condition.²⁵

MECHANISM OF SPLENIC CONGESTION

The absence of any obstruction in the portal bed is too frequent to be considered an insignificant exception, it forces one to the conclusion that an obstacle to the venous return from the spleen cannot be the first and common cause of the Banti syndrome in all cases and that the

24 Davies, J. C. Splenic Anaemia and Portal Thrombosis, *Lancet* **2** 498 (Sept 8) 1928.

25 Onsy, A. B. The Pathogenesis of Endemic (Egyptian) Splenomegaly, *Tr. Roy. Soc. Trop. Med. & Hyg.* **30** 583 (April) 1937. Shafi, A. M. Historical Review of Egyptian Splenomegaly and Allied Conditions, *J. Egyptian M. A.* **19** 561 (Oct), 631 (Nov), 652 (Dec) 1936.

opinion to the contrary, still held by the majority of authors,²⁶ should be discarded as contrasting with the pathologic evidence at present available

A few hypotheses have been submitted to explain the congestion independently from an obstruction in the portal bed. Greppi and Cesaris Demel²⁷ stated the belief that the splenic engorgement was the consequence of the decreased contractility of the capsular and trabecular framework of the spleen. This was based on the opinion that the contraction of the intrinsic muscular framework of the spleen regulated the outflow of splenic blood. But muscle fibers are scarcely distributed in the human spleen, and the efficacy of their contraction is doubtful.²⁸ Also the rhythmic changes of splenic volume are caused not by a rhythmic contraction and relaxation of the smooth muscular framework of the spleen but by rhythmic variations in the blood flow.²⁹ By others³⁰ it has been suggested that the veins of the portal bed have a contractile, arterial-like function which actively helps the blood to overcome the peripheral resistance of the liver. Thus, it was suggested that the insufficiency of this function is the cause of the congestion. But, though portal vessels are rich in muscle fibers and endowed with high contractility, there is no evidence of their arterial-like activity. Nor could it be demonstrated that lesions of the walls of the portal vessels preceded the splenic congestion.

26 Castle, W. B., and Minot, G. R. *Pathological Physiology and Clinical Description of the Anemias*, New York, Oxford University Press, 1936, pp. 117-121. Magner, W. *A Textbook of Hematology*, Philadelphia, P. Blakiston's Son & Co. 1938, p. 232. Rousselot.^{6c}

27 Greppi, E. Splenomegalie congestizie (da atonia) significato, patogenesi e cura, *Boll. Soc. med.-chir.*, Catania **3** 446, 1935. Cesaris Demel, A. Considerazioni sull'atonia dell'apparato muscolare contrattile della milza nella patogenesi di alcune splenomegalie, *Baglivi* **1** 200, 1935.

28 (a) Maximow, A. A., and Bloom, W. *A Textbook of Histology*, ed. 3, Philadelphia, W. B. Saunders Company, 1938, p. 269. (b) Giunti, G. L'apparato elastico-muscolare dello stroma splenico in diverse condizioni patologiche (considerazioni sulla splenocontrazione e sulla splenoriduzione), *Arch. ital. di anat. e istol. pat.* **10** 123 (June) 1939.

29 Grindlay, J. H., and Herrick, J. F. The Blood Reservoir Function and Rhythm of the Spleen. Preliminary Report of an Experimental Study, *Proc. Staff Meet., Mayo Clin.* **13** 663 (Oct. 19) 1938. Grindlay, J. H., Herrick, J. F., and Mann, F. C. Measurement of the Blood Flow of the Spleen, *Am. J. Physiol.* **127** 106 (Aug.) 1939. Grindlay, J. H., Herrick, J. F., and Baldes, E. G. Rhythmicity of the Spleen in Relation to Blood Flow, *ibid.* **127** 119 (Aug.) 1939. Bariéty, M., and Kohler, D. Excitations uretrales et changements du volume de la rate chez les chiens normaux, yohimbinisés, atropinés, cocaïnés et eserinisés, *Compt. rend. Soc. de biol.* **127** 972, 1938.

30 Cellina, M. Splenomegalie da alterato circolo portale e splenomegalie tromboflebitiche, *Gior. di clin. med.* **15** 615 (July 20) 1934. de Castro and dall'Acqua, G. Osservazioni sulla splenomegalia tromboflebitica primitiva, *Atti Soc. lomb. di chir.* **3** 845, 1935.

To explain the genesis of splenic congestion, some other facts must be remembered 1 The afflux of blood to the splenic pulp is regulated chiefly by the malpighian arteries and by other arteries in the pulp and in the trabeculae, which are rich in muscular tissue It was noted by Knisely³¹ that the contraction of the malpighian arteries is strong enough to obliterate their lumen There are other vascular systems acting as capillary regulators which determine the afflux and the deflux of blood to and from the sinuses (Knisely³¹), but in the general economy of the splenic circulation, their importance is likely to be a local one, as their insufficiency could be counterbalanced by the muscular system of bigger arteries 2 The output of splenic blood is limited by the peripheral resistance of the liver, which normally is small, being overcome by a portal pressure of 8 to 10 mm of mercury But when the splenic output increases above a definite amount, the blood can overcome the hepatic resistance only if the portal pressure rises adequately 3 In instances of Banti splenomegalies, lesions of the malpighian and other small arteries—the most evident signs of which are periarteriolar hemorrhages and periarteriolar fibrosis—have constantly been found, even in early stages of the disease

This last point gives enough evidence, I believe, to warrant the assumption that the small splenic arteries are the seat of early lesions In consequence, their function of adjusting the intake of blood is altered, and blood enters the spleen in an increased quantity, which cannot be discharged through the hepatic resistance under normal conditions Thus, the spleen becomes congested and widens, the elastic tension of the supporting framework increases, raising the pressure of the out-flowing blood This condition permits an increased amount of blood to pass through the small hepatic vessels

The spleno hepatic circulation, altered in consequence of the insufficient regulating function of diseased splenic arterioles, is subject to a compensatory rise of venous pressure, which is a direct result of the splenic dilatation

Becoming chronic, the splenic engorgement may be directly responsible for some lesions of the splenic pulp (fibrosis or hyperplasia), while the venous hypertension causes dilatation of splenic and portal veins and, eventually, their thrombosis Further consequences are degenerative changes in the liver cells, which may not be extraneous to the genesis of portal cirrhosis

Subsequently, either splenic thrombosis or cirrhosis of the liver, or both together aggravate the portal congestion and may dominate the

31 Knisely, M H Spleen Studies I Microscopic Observations of the Circulating System of Living Unstimulated Mammalian Spleens, *Anat Rec* 65 23 (April 25) 1936, II Microscopic Observations of the Circulating System of Living Traumatized Spleens and of Dying Spleens, *ibid* 65 131 (April 25) 1936

further development of the disease. They are complications or associated morbid conditions and not the first cause of the congestion, because—as should always be remembered—splenic congestion may be found independent of either.

Obviously, the favorable effect of splenectomy or of ligation of the splenic artery (Gieppi¹⁰⁷ and Kemp³²), which often, besides relieving the general and hematologic conditions, diminishes the tendency to gastroesophageal hemorrhages and ascites, is due to the removal of the primary cause of portal congestion. But some failure, often cited in the literature,³³ should have been foreseen, as splenectomy cannot remove the eventual thrombosis of the cirrhosis, nor can it always modify the state of gastroesophageal varices³⁴ or of the widespread dilatation of submucous and subserous small vessels of the esophagus and the stomach, which is frequently seen in cases of this kind (Ravenna⁷ and Fiessinger, Albeaux-Fernet and Varay³⁵).

COMMENT

It seems to me particularly significant that the present conception of primary splenic congestion is based on the undisputed presence of lesions in the small splenic arteries. Their fibrosis had been described by Banti¹, the presence of regressive lesions in their walls and of endoarteritis had been noted by Gamna¹³ and by myself⁷. The siderotic nodules themselves are the direct consequence of periarteriolar hemorrhages, as pointed out in 1902 by Marini,³⁶ the first author who described such lesions, and his interpretation was substantially confirmed by successive observers³⁷. The significance of arteriolar lesions in the

32 Kemp, R. Recurrent Haematemesis in Banti's Disease, *Brit M J* **1** 222 (Jan 29) 1938.

33 Pemberton, J deJ. Results of Splenectomy in Splenic Anemia, Hemolytic Jaundice and Haemorrhagic Purpura, in *Collected Papers of the Mayo Clinic and the Mayo Foundation*, Philadelphia, W. B. Saunders Company, 1931, vol 23, p 539, *Ann Surg* **94** 755 (Oct) 1931.

34 Hines, L. E., and Fitzgerald, B. Splenomegaly of the Banti Type. Report of a Case with Postmortem Observations Four Years After Splenectomy, *Arch Path* **26** 155 (July) 1938. Kemp³² Greenwald, H. M., and Wasch, M. G. The Roentgenologic Demonstration of Esophageal Varices as a Diagnostic Aid in Chronic Thrombosis of the Splenic Vein, *J Pediat* **14** 57 (Jan) 1939.

35 Fiessinger, N., Albeaux-Fernet, and Varay, A. A propos des hémorragies persistantes après splénectomie, *Bull et mem Soc med d hop de Paris* **54** 494 (March 18) 1938.

36 Marini, G. Sopra un caso di splenomegalia con cirrosi epatica, *Arch per le sc med* **26** 105, 1902.

37 Gandy, C. Lesions particulieres de la rate en un cas de cirrhose biliaire, *Bull et mem Soc anat de Paris* **80** 872, 1905. Eppinger³⁴ Gamna¹³ Christeller, E., and Puskeppelles, M. Die periarteriellen Eisen- und Kalkinkrustationen in der Milz, *Virchows Arch f path Anat* **250** 107, 1924. de Vecchi

mechanism of congestion, however, had never been considered before in human pathology, but recently Greppi¹⁰ and Lenzi,³⁸ accepting the arguments discussed in my previous paper, admitted that the first lesion responsible for the splenic congestion might be an arteriolar one. Some experimental attempts to produce active congestion of the spleen were made by Henschen and Howald.^{38a} They denervated the spleen of 3 dogs, in 2 of which splenomegaly was obtained. In view of their importance, these experiments should be repeated and enlarged, with the study of the alterations, if any, secondarily produced in the portal circulation and in the liver itself.

Episodes of Gastroesophageal Hemorrhages and Ascites—Often this frequent and serious event in the course of the Banti syndrome puzzled the physicians by whom it had been attributed to an organic obstacle in the portal bed, which could not be found at the necropsy.³⁹ Hemorrhages and ascites may depend on the breakdown of the portal circulation, due to an anatomic obstacle (thrombophlebitis or cirrhosis), as well as to the progress of arteriolar lesions in the spleen and to a transitory increase of hepatic resistance, due to digestive or cardiac exigencies.

In many cases ascites appeared and disappeared quickly (Frugoni^{3e}), and I think that this fact is rather against the idea of ascribing the condition to a definite anatomic obstacle, such as that represented by thrombosis or cirrhosis. The influence of digestive requirements on splenic circulation is great indeed, as it is proved by the increase of splenic volume during the normal digestive process, and therefore in splenomegalic patients the relation of the hematemeses to digestive phases should be investigated with greater attention.

Splenic Shrinkage After Administration of Epinephrine—The shrinkage may depend on the stimulation of the splenic arterioles, the

and Zanotti^{9b} Fasiani, G. M., and Oselladore, G. Essai de reproduction experimentale des nodules de Gandy-Gamna, *Presse med* **37** 1136 (Aug 31) 1929. Jaeger, E. Ueber Stauungsmilz, *Verhandl d deutsch path Gesellsch* **26** 334, 1931, Milzbau und Kreislaufstörung, *Virchows Arch f path Anat* **299** 531 and 552, 1937. Alexandre, A., and Valducci, E. Fattori che determinano le incrostazioni siderotiche della milza nei focolai sclerosiderotici, *Pathologica* **27** 321 (May 30) 1935.

38 Lenzi, F. Sindrome Bantiana-splenomegalia fibroso-congestizia prevalentemente fibrosa-Contributo clinico-Ipotesi patogenetiche *Haematologica* **22** 47, 1940.

38a Henschen, C., and Howald, R. Die anatomischen und klinisch-physiologischen Folgen der operativen Entnervung der Milz. Experimentelle Untersuchungen, *Arch f klin Chir* **157** 667, 1929.

39 Cellina²⁹ de Castro and dall'Acqua²⁹ Lucchi, G. Morbo di Banti a lunghissimo decorso e splenomegalia tromboflebitica con trombosi della vena mesenterica superiore, *Riv di clin med* **35** 421 (July 15) 1934.

constriction of which decreases the intake of blood. Thus the shrinkage is due to the elastic retraction of the supporting framework. This conception, suggested by Colombi⁴⁰ and Villa,^{20a} was adhered to by a detailed study of the musculature in the human spleen by Giunti.^{28b} It is supported also by the evidence collected by Grindlay, Herrick and Baldes²⁹ in their experiments on the blood flow of the spleen. But it has not yet been noted that, if this mechanism be true, epinephrine should decrease the pressure in the splenic vein instead of increasing it. I do not know of any instance in which the pressure in the splenic vein was measured before and after injection of epinephrine, but the fact that the splenic shrinkage due to epinephrine never produced gastrointestinal hemorrhages, even when tried in patients who either previously or subsequently suffered from spontaneous gastrointestinal hemorrhages, speaks rather against the idea of ascribing the splenic reduction to an active contraction of the muscular framework. Obviously, an immediate episode of hemorrhage should have been a frequent consequence if the epinephrine compressed the spleen and raised the portal pressure.

This mechanism also makes easy to understand why the splenic shrinkage may be of the same degree both when an obstructive factor is present and when it is lacking.^{40a} If the epinephrine influenced the regimen of outflow, by actively expressing the blood from the spleen, a difference should have been noted under these two conditions.

A definite proof that in cases of splenic congestion epinephrine does not raise the portal pressure and a further indirect argument on its mechanism of action may be obtained by measuring the splenic venous pressure during surgical interventions. I hope that this will be tried in the near future.

As to the human spleen, the term "contraction" is, I believe, inadequate and probably incorrect, it may advantageously be substituted by "reduction" or "shrinkage," which merely describes the fact of the variation in size, without suggesting any determined mechanism.

Ascoli (Epinephrine) Therapy—That the size of the spleen could be permanently reduced by intravenous injections of epinephrine was

40 Colombi, C. La separata funzione del duplice substrato contrattile della milza, *Atti Soc. lomb. di med.* **2** 615, 1934.

40a Greppi, E. La negatività della splenocontrazione adrenalinica non esclude la natura sanguigna del tumore di milza, *Pol. clinico (sez. prat.)* **43** 53 (Jan. 13) 1936. Villa^{20a} Grenet, H., in discussion on Weill-Halle, P., de Gaudard d'Allaines, and Papaioannou, A. Hematemese et melaena chez un enfant de neuf ans. Splénomégalie ancienne. Arrêt des hemorrhagies après splénectomie, *Bull. et mem. Soc. méd. d'hop. de Paris* **53** 1481 (Dec. 6) 1937.

demonstrated by Ascoli, d'Alessandro, Riolo and Pizzillo,⁴¹ who suggested injections of epinephrine hydrochloride as a new method of therapy for chronic malarial splenomegaly. Its favorable effect was confirmed by many authors.⁴² The attempt to influence other splenomegalies with the same method is a logical consequence. The best results may be anticipated in cases of the Banti syndrome, in which the vascular factor plays such a great part.

I have tried this treatment on 3 patients, by injecting 0.01 mg. to 0.10 mg. of epinephrine hydrochloride intravenously on each of twenty successive days, as suggested by Ascoli and his associates. Two of these patients were suffering from a cryptogenetic Banti syndrome in an early stage. The spleen reached to about 3 inches (8 cm.) below the costal margin, and the liver was practically normal. A marked decrease of splenic size was obtained, without, however, influencing the general conditions. But the leukocytic count diminished quickly, in 1 case from 2,500 to 650 per cubic millimeter. Therefore, it was believed that further delay might be dangerous, and splenectomy was performed. The postoperative course was uneventful. Both patients were followed up for about a year, and they remained in good general and hematic condition. The third patient had an enormous splenomegaly and hypertrophic hepatic cirrhosis, years before he had suffered from malaria, and the serologic reactions proved that he was syphilitic. His poor condition contraindicated splenectomy. Antisyphilitic treatment together with Ascoli therapy caused permanent decrease of splenic size, a slight decrease of hepatic volume and satisfactory improvement of the general state.

Further experience is required, but I wish to suggest that it may be worth while to try Ascoli's method of treatment in cases in which surgical intervention on the spleen offers few chances of success. If the epinephrine lowers the portal pressure, this treatment might also decrease the danger of serious hematemesis in nonoperable patients.

41 Ascoli, M. Sulla cura dell'infezione malarica cronica, *Riforma med.* **52**: 351 (March 14) 1936. d'Alessandro, G. Sulla cura di M. Ascoli della infezione malarica, *Riv. di malariol.* (sez. I) **16**: 290, 1937. Riolo, P. Sulla cura di M. Ascoli della infezione malarica, *ibid.* **16**: 34, 1937. Pizzillo, G. Sulla cura di M. Ascoli della infezione malarica, *ibid.* **17**: 404 and 441, 1938.

42 Gosio, R. Sondaggio di contrattilità della splenomegalia malarica e trattamento adrenalínico della stato malarico, *Riv. di malariol.* (sez. I) **16**: 123, 1937. Mosna, E. Sulla cura di M. Ascoli della infezione malarica, *ibid.* **17**: 126, 1938. Nucciotti, L. Ricerche sulla terapia adrenalínica nella malaria estivo-autunnale primitiva, *ibid.* **17**: 131, 1938. Canova, F. Associazione chinino-adrenalínica nel trattamento della malaria acuta, *ibid.* **16**: 31, 1937. Froilano de Mello, J. Experimental Studies on the Treatment of Malarial Splenomegalies by the Method of Ascoli, *South African M. J.* **12**: 835 (Nov. 26) 1938.

SUMMARY AND CONCLUSIONS

Evidence has been accumulating which supports the view that Banti splenomegaly is largely due to splenic congestion and that this congestion is not dependent on an obstructive factor in the portal-venous bed. It is suggested that the congestion may be due to primary lesions of the small splenic arteries which regulate the blood flow into the spleen ("primary active congestion").

The human spleen should be considered as an elastic rather than as a contractile organ. Its variations in size depend on variations in volume of the inflowing blood, rather than on active contractions of the smooth muscle of its supporting framework.

From a mechanical point of view, the spleen might be defined as an automatic controller which regulates the pressure of the splenic venous blood in order to maintain the balance between the volume of inflowing blood and the amount which can be discharged through the hepatic resistance. Normally, and within certain limits, in pathologic conditions, the splenic elasticity guarantees a pressure sufficient to secure the further progress of venous portal blood. Congestive splenic enlargement is therefore a mechanism to counterbalance either increased volume of portal blood or increased peripheral resistance to the discharge of a normal amount of blood.

The Banti syndrome is a symptom complex dominated by chronic fibrocongestive splenomegaly, accompanied by portal hypertension and complicated by, or associated with, hepatic cirrhosis or thrombosis of the splenic and portal veins. It may depend on various causative agents, either infective or toxic. A scheme for its etiologic classification is presented.

The splenic changes of Banti syndrome are probably due to primary lesions of the splenic arterioles, the regulating power of which becomes insufficient to control the inflow of blood. The consequent congestive splenomegaly is the cause of the circulatory disturbance in the portal bed. Secondly, hepatic cirrhosis and venous thrombosis may aggravate the state of portal circulation.

Progress in Internal Medicine

GASTROENTEROLOGY

REVIEW OF LITERATURE FROM JULY 1939 TO JULY 1940

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The widespread interest in gastroenterologic problems and their clinical importance is evidenced by the multiplicity of articles appearing in the world literature on all phases of the physiology of the alimentary tract, normal and abnormal, and the therapeutic applications directed thereto. Some new data have been added, particularly to the knowledge of the physiologic response of the digestive tract to various drugs, many of which are actively employed at present. In this review allusion will be made to strictly new discoveries and to new applications of old principles. It will also be my purpose, however, to call attention to many articles of clinical importance for the sake of reemphasizing recognized or partially recognized concepts of gastrointestinal disease.

PHYSIOLOGIC ASPECTS

Interest continues in the various factors influencing gastric secretion. In fact, attempts are still being made to obtain a satisfactory normal gastric secretory curve by varying technics. Wilhelmj and Sachs¹ still pursue their studies of gastric secretion following a test meal consisting of a specially prepared solution of Liebig's meat extract and a standard amount of phenolsulfonphthalein (phenol red). They believe that after such a test meal it is possible to determine what proportion of a given sample is fluid of the test meal remaining in the stomach and what proportion is due to secretions. The total secretions entering the stomach can be separated into acid and nonacid fractions, and the acidity of the total secretions can be determined independent of the acidity of the mixed gastric contents. Multiple curves on given subjects show a rather remarkable agreement, and the amount of acid secretion is usually constant in the same person. The increase in nonacid secretion due to regurgitation from the duodenum varies considerably even in the same

1 Wilhelmj, C M, and Sachs, A. The Characteristics of the Normal Human Gastric Secretory Curve Using an Improved Gastric Test Meal, *Am J Digest Dis* 6 529, 1939

person, with corresponding variation in the acidity of the total secretion entering the stomach. One interesting observation was made on the effects of mild acute alcoholism on the "morning after" in subjects on whom several curves had previously been obtained under normal conditions. There seemed to be a definite increase in the amount of acid secretion and a decrease in the amount of nonacid secretion, with a consequent elevation of the acidity of the total gastric contents. Values obtained among medical students appeared to be definitely higher than those noted previously in a group of free clinic patients. The authors suggest the possible importance of such a finding in relation to the higher incidence of duodenal ulcer in professional men and business executives. As a result of their studies Wilhelmj and Sachs² suggest that the final control of gastric acidity depends on at least two factors, namely, acid inhibition, which controls primarily the acidity of the gastric contents and duodenal regurgitation, which controls primarily the acidity of the total secretions entering the stomach. Either mechanism may vary in different normal subjects and may fail in the presence of disease. They point out, however, that there still are several unknown factors, which make it difficult to establish any absolute figures for maximal and minimal secretory levels.

Among other factors influencing gastric secretion, that of advancing years has been recognized for some time. Bloomfield,³ who has already called attention to the importance of this phenomenon, reports observations on 5 subjects who were reexamined after intervals of over ten years. Of the 5 subjects, 3 showed gastric secretion practically identical to that observed ten years previously, 1 showed a slight decline of acidity but not of volume of secretion, and 1 showed a diminution both in volume and in amount of acid. As Bloomfield points out, it is of real importance to carry out further and similar studies over long periods. He suggests the importance of associated gastroscopic observations to determine, if possible, whether any visible change in the mucosa occurs which can be correlated with alterations in gastric secretion. Why some normal persons preserve their gastric secretion unaltered over many years while others show a rapid decline in secretory activity is still entirely obscure. Bloomfield⁴ also studied the effect of suggestion of a palatable food on gastric secretion. In these observations the food was not actually seen, smelled or tasted, but in 12 of 14 cases suggestion alone

2 Wilhelmj, C. M., and Sachs, A. The Physiological Control of the Normal Human Gastric Secretory Curve, *Am J Digest Dis* 6:467, 1939.

3 Bloomfield, A. L. The Decrease of Gastric Secretion with Advancing Years. Further Observations, *J Clin Investigation* 19:61, 1940.

4 Bloomfield, A. L. Psychic Gastric Secretion in Man, *Am J Digest Dis* 7:205, 1940.

was followed by an acceleration of secretion, the increase in volume being much more marked than the increase in acidity, in contrast to the stimulation normally observed after administration of histamine. The author explains this difference on the basis that psychic stimulation is transmitted to the stomach by way of the fibers of the vagus nerves, whereas histamine acts directly on the secretory cells. Such a conception is entirely comparable to the increase in motor activity to be noted under the fluoroscope when appetizing food is discussed.

The significance of gastric acidity after histamine stimulation was made the basis of a study by Ruffin and Dick⁵ in a series of 2,877 gastric analyses. The writers made extensive studies of the acid values in this large group, of which 1,917 were normal persons and concluded that there is a much wider range of variation in normal persons after administration of histamine than after use of the Ewald meal. They point out the fact, still not too generally accepted, that there is no such thing as a normal level of gastric acidity. The tremendous variation in acid values obtained by these and other investigators clearly illustrates the fallacy of the terms "hyperacidity" and "hypoacidity" except as implying relative levels of no real clinical significance. As in other studies, a significant difference in gastric acidity between men and women was observed. The mean for women was much lower than that noted for men. Confirmation of recent studies was obtained that there is no significant variation from the normal in patients suffering from rheumatoid or hypertrophic arthritis. The incidence of achlorhydria in this group of persons increases with age, as has now repeatedly been shown. The condition was frequently found in cases of cancer of the stomach and of pellagra, and it is of extreme interest that in 24 patients with active duodenal ulcers no free acid could be demonstrated after administration of histamine. The latter finding is highly suggestive in its implication that gastric hydrochloric acid at best is merely one important factor in the activity of peptic ulcer.

Katzenelbogen, Loucks and Gantt⁶ performed experiments on dogs with Pavlov pouches in an attempt to condition gastric secretion to histamine. Their results were quite the reverse of those already alluded to as obtained by Bloomfield with human subjects. These authors found it impossible to elaborate a conditioned secretory reflex to histamine in their animals, and they explained such a failure as due to the fact that histamine acts peripherally. They compared, quite properly, the difference between the salivary secretion following the use of

5 Ruffin, J. M., and Dick, M. The Significance of Gastric Acidity After Histamine Stimulation. A Statistical Study of 2,877 Gastric Analyses, *Ann Int Med* **12** 1940, 1939.

6 Katzenelbogen, S., Loucks, R. B., and Gantt, W. H. An Attempt to Condition Gastric Secretion to Histamine, *Am J Physiol* **128** 10, 1939.

pilocarpine hydrochloride, which is entirely due to peripheral stimulation, and that following the injection of morphine, which can be conditioned and which is known to have a definite central action

An unusual action of histamine is suggested by the experiments of Ivy and Bachrach⁷ as a possible explanation of the continuous secretion of gastric juice seen in some patients with ulcer and in patients with some other abnormal conditions. These authors noted that in 3 Mann-Williamson dogs with Pavlov pouches there was definite continuous hypersecretion, and in 1 animal there was definite hypersecretion in response to a meal. The gastric secretory mechanism reacted to atropine as though a portion of the secretory stimulus were histamine, the implication being that there had been an elaboration of histamine by an irritated or inflamed mucous membrane.

The favorable effect of pregnancy on the activity of ulcer has been noted by various investigators. Labate⁸ reports studies on the effect of pregnancy on gastric secretion in 56 patients. For none of this group of pregnant women were the figures for gastric acidity above the so-called normal range, and for one fourth of the entire group the values were very low or complete achlorhydria was noted after administration of histamine. It is possible that the incidence of complete achlorhydria was no greater, however, than that to be anticipated in this particular age group. It is of interest that the average red blood cell count and hemoglobin concentration apparently showed a decrease as the gastric acidity diminished, although the author did not attempt to attribute the appearance of such anemia solely to alterations in gastric acidity. It is unfortunate that he did not complete his study by making similar examinations of the same group of subjects after delivery. Had such a study been made, the probable role of the endocrine factors operative during pregnancy might have been more clear.

Because of observations similar to those mentioned, such as those of Sandweiss and others, Culmer, Atkinson and Ivy⁹ made studies on the effect on gastric secretion of the gonadotropic fraction of the urine of pregnant women. This substance was administered parenterally, and the gastric secretory response to a test meal was measured in 5 female dogs with Pavlov pouches. The authors chose the gonadotropic fraction of the urine of pregnant women for a study of the cause of the reduced acidity of gastric contents during pregnancy because this sub-

7 Ivy, A. C., and Bachrach, W. H. An Abnormal Mechanism for the Excitation of Gastric Secretion in the Dog, *Am. J. Digest. Dis.* **7** 76, 1940.

8 Labate, J. S. The Effect of Pregnancy on Gastric Secretion, *Am. J. Obst. & Gynec.* **38** 650, 1939.

9 Culmer, C. U., Atkinson, A. J., and Ivy, A. C. Depression of Gastric Secretion by the Anterior Pituitary-Like Fraction of Pregnancy Urine, *Endocrinology* **24** 631, 1939.

stance is produced in great quantities in women during the earlier period, when gastric secretion is reported to be most depressed, whereas in the dog it is not thought to be produced, and gastric secretion seems not to be depressed during pregnancy. After suitable control tests were made following injections of gonadotropic substance, significant to marked decreases in the volume of acid output occurred each day during a five day period of treatment. In 4 of 7 instances the secretory response returned to normal almost immediately. The activity of the gonadotropic substance was evidenced in that "estrus" occurred in 4 of 8 instances after its administration. The authors conclude that the gonadotropic fraction of the urine of pregnant women contains a substance which depresses the gastric secretory response of a dog to a meal, although they admit that the nature of the substance and its mechanism of action are still uncertain. Elsewhere Ivy¹⁰ discusses the probability that the ulcer-preventing principle known to be present in urine is distinct from the gonadotropic substance in the urine of pregnant women. Extracts prepared from the urine of patients with peptic ulcer have been reported by Sandweiss to be lacking in the ulcer-preventing factor and by Freedman to contain the usual amounts of the principle that inhibits gastric secretion. Experiments are in progress at present to determine, if possible, the nature of the inhibiting factor found in urine ("uro-gastione") and its identity, if this exists, with the inhibitory principle known to be present in duodenal extracts ("enterogastione").

Further observations on the effect of insulin on gastric secretion are supplied by the studies of Horstmann,¹¹ who found on examination of 10 schizophrenic patients that in the presence of insulin coma a considerable rise in the acidity of the gastric secretion occurs after an initial fall. The rise begins after the level of blood sugar has reached its low phase, and the fall occurs after oral administration of cane sugar or dextrose and intravenous administration of dextrose in doses which terminate the effect of insulin. He also compared the effect of insulin with that of histamine as a stimulant to gastric secretion in 6 other patients, 5 of whom had achylia to alcohol test meals. Insulin proved to be more effective than histamine in causing a secretion of acid gastric juice and was said to produce acid gastric secretion when histamine had no effect.¹²

Numerous other studies on the stimulating or inhibiting effect of various substances on gastric secretion are reported. Shay and his

10 Ivy, A. C. A Substance in the Urine Which Inhibits Gastric Secretion, editorial, *Am J Digest Dis* **7** 49 1940.

11 Horstmann, P. Investigation on Effect of Insulin on Gastric Secretion, *Ugeskr f Læger* **101** 935 1939.

12 Horstmann, P. Insulin Compared with Histamine as Stimulant of Gastric Secretion, *Nord med (Hospitaltid)* **4** 3566, 1939.

collaborators,¹³ for example, studied the effect on total gastric secretion of the instillation of neutral fat, fatty acids and soaps into the duodenum. A rather striking depression of all gastric secretory functions was noted, involving the production of acid, chloride and enzymes. The depression of secretion continued for a considerable period but usually was followed by a rise in all values. There appeared to be a difference between the motor and the secretory responses following such duodenal instillations and even between the secretion of acid and that of enzymes. Because the introduction of fatty substances into the duodenum prevented the expected stimulation of gastric secretion during insulin hypoglycemia, the authors conclude that this depression of gastric secretion represented chiefly an effect on the neurogenic phase of gastric activity. Such a conclusion, however, seems highly speculative, as they were unable by such measures to prevent a rise in gastric secretion following injection of histamine.

Pickett and Van Liere¹⁴ noted in dogs with Pavlov or Heidenhain pouches that increasing degrees of anoxia caused proportional decreases in the volume of gastric secretion. Partial pressures of oxygen, corresponding to 8,000, 14,000, 18,000 and 24,000 feet, respectively, were employed. Gastric secretion in the animals with Heidenhain pouches was affected by much less severe degrees of anoxia than in the Pavlov group, a reduction in chloride being noted at an oxygen equivalent of 14,000 (94 mm of mercury). This indicates that in part, at any rate, the reduction in gastric secretion associated with anoxia is due to vagal stimulation, and it is well known that anoxia is capable of stimulating the medullary centers.

Attempts to determine some correlation between the carbon dioxide content of the plasma and gastric acidity were made by Taylor and Michael.¹⁵ Lowering of the plasma carbon dioxide to a level of 26 volumes per cent by the feeding of ammonium chloride caused no decrease in the free acid in Pavlov pouches in animals, although there was a great increase in the pouch secretion, which was attributed to a coincidental water intake due to the thirst produced by ingestion of ammonium chloride. Dehydration was effective in reducing the amount of pouch secretion but produced little or no change in gastric acidity.

13 Shay, H., Gershon-Cohen, J., and Fels, S. S. The Role of the Upper Small Intestine in the Control of Gastric Secretion. The Effect of Neutral Fat, Fatty Acid and Soaps, the Phase of Gastric Secretion Influenced and Relative Importance of the Psychic and Chemical Phases, *Ann Int Med* **13** 294, 1939.

14 Pickett, A. D., and Van Liere, E. J. The Effect of Anoxia on Gastric Secretion from Pavlov and Heidenhain Pouch Dogs, *Am J Physiol* **127** 637, 1939.

15 Taylor, F. W., and Michael, A. C. Relation of Blood Carbon Dioxide and Dehydration to Gastric Acidity, *Am J Digest Dis* **7** 67, 1940.

Arrieff¹⁶ found that administration of sodium bromide to man caused displacement of the chloride ions in gastric secretion, as in the blood and other tissues, the chloride ion being displaced from 25 to 50 per cent. No significant changes in titratable acidity were noted, and there appeared to be no important retarding effect on peptic or tryptic digestion. Nutritional disturbances were noted only when there was anorexia or toxicosis.

Animal experiments on the effect of the barbiturates on gastric secretion were carried out by Coffey, Koppanyi and Linegar.¹⁷ Using intravenous injections of sodium barbiturate and sodium amytal in large hypnotic and anesthetic doses, they noted a reduction in gastric secretion with a prompt return to normal after hypnotic doses and delayed return after anesthetic doses. The maximal postcibal excretion of the drugs in the gastric juice was approximately 5 per cent.

Exposure of the gastric mucosa to various solutions and its effect on the gastric response to histamine was studied by Mann and Mann.¹⁸ Transitory achlorhydria was produced in dogs by introduction of a dilute solution of mercuric and cupric salts. Much greater concentrations of lead, manganese and zinc produced no effect. The use of quinone caused inhibition of gastric secretion, while hydroquinone and resorcinol had no effect in concentrations one hundred times as great. Brilliant green and crystal violet inhibited gastric secretion.

In addition to endocrine factors influencing gastric secretory activity, various observations have been made on the effect of specific diseases in this regard. That cholecystic disease tends to be associated with diminished gastric secretion of acid has been noted by various observers. The studies of von Muranyi¹⁹ on 64 patients with gallstones are of some interest, however, as gastric secretory curves taken after use of the Einhorn fraction test meal showed no uniform results prior to operation. Great individual differences were observed, and there was no evidence that gastric analyses were of diagnostic value in this condition. One fourth of the subjects had achylia or hypoacidity, but no significant discoveries were made in association with such complications as obstructive jaundice and acute cholecystitis. It is of interest that subsequent observations, made a year after cholecystectomy, revealed apparently normal

16 Arrieff, A. J. Effect of Sodium Bromide on Nutrition and Gastro-Intestinal Tract of Epileptic Patient, *J. Lab. & Clin. Med.* **25** 19, 1939.

17 Coffey, R. J., Koppanyi, T., and Linegar, C. R. The Effect of Barbiturates on Digestive Secretion, *Am. J. Digest. Dis.* **7** 21, 1940.

18 Mann, F. D., and Mann, F. C. An Experimental Study of Some Chemical Inhibitors of Gastric Acidity, *Am. J. Digest. Dis.* **6** 322, 1939.

19 von Muranyi, L. Modifications in Secretions of Gastric Juice in Gallstone Diseases Before and After Extirpation of Gallbladder, *Beitr. z. klin. Chir.* **170** 513, 1939.

values in nearly three fourths of the cases, whereas the original observations had revealed so-called normal values in only about 40 per cent

Inconstant results in studies on the nature of the gastric secretion present in association with rheumatoid arthritis have been obtained since the original observations of Woodward and MacKenzie, who apparently showed in 1912 that gastric achylia is a frequent associated finding. Studies reported by Edstrom²⁰ of 432 patients with this disease showed that nearly 20 per cent of the group had achylia refractory to histamine and that an additional 10 per cent had a very low level of gastric secretion. The achylia proved to be more frequent in cases of more severe involvement but was independent of the duration of the disease. Of 50 patients of this group subsequent examinations were made after long intervals, and it is of interest that only 12 of 23 patients with achylia at first refractory to histamine continued to show no gastric secretory response to stimulation with the drug. It must not be forgotten, however, that variations in the response to histamine also occur in normal subjects, as has been shown by Schiff, Palmer and others, the stomach at times being completely refractory and at other times entirely normal.

The relation between carcinoma of the stomach and the known reduction of gastric acidity has long been a matter for speculation. The observations of Brunschwig and Clarke²¹ are of interest in this respect. Gastric analyses were made of a group of 70 patients with cancer of the stomach verified by operation or necropsy. Sixty per cent of the group exhibited achlorhydria, and an additional 15 per cent had hypochlorhydria. It is to be pointed out, however, that less than half of the patients were tested after the use of histamine, and it is probable, as the authors agreed, that the incidence of achlorhydria in the series would have been appreciably reduced had histamine been employed. A fairly accurate measure of the amount of carcinomatous tissue was obtained in each instance, and it was found impossible to demonstrate any definite relation between the size of the tumor and achlorhydria. Actually, the surface area of the cancer in patients with achlorhydria averaged much less than half of that noted in patients with normal types of secretion. Neither was there any evidence to indicate a definite relation between the histologic type of the cancer and the quality of gastric secretion, although in this small group there seemed to be a suggestion that the scirrhous type of carcinoma was accompanied by achlorhydria less frequently than were the other types.

20 Edstrom, G. Gastric Secretion and Basal Metabolism in Chronic Rheumatic Arthrides, *Acta med Scandinav* **99** 228, 1939.

21 Brunschwig, A., and Clarke, T. H. Histologic Structure of Carcinomas of the Stomach and Quality of Gastric Secretions, *Ann Int Med* **13** 1001, 1939.

Brunschwig and his associates²² have amplified work previously reported on the depressant effect of gastric juice obtained from patients with pernicious anemia. Intravenous injection of gastric juice from 18 patients with pernicious anemia resulted in a marked transitory depression of pouch secretion in dogs and in achlorhydria in 90 per cent of samples taken, as contrasted with the results obtained by injection of gastric juice obtained from 34 hospital patients without pernicious anemia or malignant disease. With the latter, gastric secretory inhibition was noted in less than one fifth of the observations. These investigators also showed²³ that samples of achlorhydric gastric juice taken from patients with cancer of the stomach produced a similar inhibition of gastric secretion in nearly 80 per cent of the experiments. The significance of such findings is far from clear as gastric inhibition was noted after use of material from patients not suffering from pernicious anemia or cancer, although previous control experiments had indicated that gastric juice from apparently normal persons has no inhibitory effect.

Attempts to correlate vitamin C deficiency and achlorhydria fail to show any correlation. Nordstrom²⁴ was unable to demonstrate any reduction of the acidity of gastric juice following injection of histamine after production of an absolute deficiency vitamin C in guinea pigs. Herrin²⁵ was unable to demonstrate any change from normal in the free and total acids in the gastric juice and the rate of secretion in response to histamine in dogs on a diet absolutely deficient in vitamin A. Subsequent administration of vitamin A to these animals produced no significant changes.

Some further light on the mechanism of secretion of hydrochloric acid in the stomach is afforded by the studies of Davenport²⁶. This investigator demonstrated in cats, rats and dogs that carbonic anhydrase is present in the parietal cells of the gastric mucosa but not to any appreciable extent in the surface epithelium of the gastric mucosa, in the chief cells or in the fundic cells. A small amount appears to be present in an unidentified cell in the pyloric antrum of the rat. In cats and rats

22 Brunschwig, A., Van Prohaska, J., Clarke, T. H., and Kandel, E. V. A Secretory Depressant in Gastric Juice of Patients with Pernicious Anemia, *J. Clin. Investigation* **18** 415, 1939.

23 Brunschwig, A., Clarke, T. H., Van Prohaska, J., and Schmutz, R. L. A Secretory Depressant in the Achlorhydric Gastric Juice of Patients with Carcinoma of the Stomach, *Surg., Gynec. & Obst.* **70** 25, 1940.

24 Nordstrom, T. Experimental Investigations of the Hydrochloric Acid Secretion in Scorbutic Guinea-Pigs, *Acta med. Scandinav.* **99** 443, 1939.

25 Herrin, R. C. Gastric Emptying Time and Acidity in Avitaminosis in Dogs, *Am. J. Digest. Dis.* **7** 164, 1940.

26 Davenport, H. W. Gastric Carbonic Anhydrase, *J. Physiol.* **97** 32, 1939, Gastric Carbonic Anhydrase in Dogs, *Am. J. Physiol.* **128** 725, 1940.

the concentration of this substance in the parietal cells is several times greater than that noted in the red blood corpuscles. The fact that there is a high concentration of carbonic anhydrase in the parietal cells leads to the supposition that carbonic acid may play an important role in the mechanism of formation of hydrochloric acid. This author²⁷ found that sodium thiocyanate inhibits the ability of carbonic anhydrase to catalyze the hydration and dehydration of carbon dioxide and inhibits secretion of acid by the gastric mucosa of dogs. He explains this inhibition of secretion by the assumption that sodium thiocyanate inhibits the carbonic anhydrase, which is a part of the secretory mechanism, and apparently shows that the rate of secretion of acid by the gastric mucosa is directly proportional to the rate of formation of carbonic acid in the secretory mechanism.

To those interested in animal experimentation, the new type of gastric pouch described by Cope and his collaborators²⁸ will be of interest. These authors confirm the previous observations that the vagal supply of the Pavlov type of gastric pouch is not intact. They describe a gastric pouch in the dog, made from the anterior wall of the body of the stomach which has the advantage of an intact autonomic nerve supply, both vagal and sympathetic, with only partial denervation of the residual portion of the stomach distal to the collecting pouch. The mechanical stimulation of secretion is reduced to a minimum by obviating the necessity of an intlying cannula, and care of the animal is greatly facilitated.

In a further study on the physiologic effects of gastric mucin, Wigodsky, Bussabarger and Fogelson²⁹ noted the effects of gastric mucin on regeneration of hemoglobin in anemic dogs. Commercial preparations of gastric mucin appeared to stimulate the production of hemoglobin in anemic dogs from 55 to 70 per cent more than could be accounted for by the amount of iron present in the preparation. However, the stimulus was not so great as that noted when beef liver was fed.

Within the past ten years experiments have been carried out on animals in an attempt to find a reliable method of detecting the presence of antianemic substances. Singer, in 1935, found that injection of normal gastric juice into old albino rats caused a characteristic increase in the number of circulating reticulocytes and concluded that the presence or

27 Davenport, H. W. The Inhibition of Carbonic Anhydrase and of Gastric Acid Secretion by Thiocyanate, *Am J Physiol* **129** 505, 1940.

28 Cope, O., MacMahon, C. E., Hagstromer, A., and Thompson, R. H. Gastric Secretion. I. A New Gastric Pouch with a Nonleaking Stoma and an Intact Nerve Supply, Description of a Two-Stage Technique Used on the Dog, *Arch Surg* **40** 717 (April) 1940.

29 Wigodsky, H. S., Bussabarger, R. A., and Fogelson, S. J. The Effect of Gastric Mucin on the Hemoglobin Regeneration in Anemic Dogs, *J Lab & Clin Med* **25** 13, 1939.

absence of the "intrinsic hematopoietic factor" in any given specimen of gastric juice could be determined readily. By similar studies, Schlicke³⁰ was unable to confirm these conclusions. Neither oral nor intramuscular injections of gastric juice and gastric juice concentrates produced any consistent or predictable changes in the number of circulating reticulocytes in rats. He concluded that the variable reticulocyte response to gastric secretion, which is nonspecific, is unreliable in detecting the presence of antianemic substances.

Various studies have been made on alterations in the motor activity of the stomach. Gordon and Singleton³¹ made observations on dogs and describe in detail two types of gastric peristalsis, the first involving all coats of the stomach, purely propulsive and with wide swings, and the second involving only the mucosa and the muscularis mucosae, its function apparently being propulsive and also having an added mixing effect on the gastric contents. As this second type of peristaltic wave passes distally, tonic changes occur in the muscularis propria.

Van Liere and Sleeth³² present an interesting review of the literature on the effects of acid and of alkali on gastric motor activity. To a series of healthy medical students known to have hydrochloric acid in their fasting gastric juice, a standard test meal was given, to which had been added a standard amount of barium sulfate. The normal emptying time was ascertained by repeated fluoroscopic examinations. There was considerable individual variation, but in any given subject motor activity appeared to be constant under the experimental conditions. It was found that therapeutic doses of hydrochloric acid produced a slight but not very significant delay in the emptying time for such subjects. On the other hand, a therapeutic dose of sodium bicarbonate (5 Gm. in 100 cc. of water) was followed by an average increase of over 16 per cent in the emptying time of the stomach. In order to determine whether the result was due to alkali or to carbon dioxide, a therapeutic dose of disodium phosphate was used, and this produced an almost identical increase in the rapidity of gastric emptying. Such a study presents more or less quantitative evidence as to the effects of therapeutic doses of commonly used acids and alkalis on the motor response of a normal stomach, but the actual mechanism involved is still not clear. The authors suggest three possible mechanisms: (1) a direct effect on the pylorus, (2) stimulation of motor activity associated

30 Schlicke, C. P. Studies on the Effect of Human Gastric Juice in the Reticulocytes of Albino Rats, *Am J Digest Dis* **7** 277, 1940.

31 Gordon, S., and Singleton, A. C. Gastric Peristalsis, *Surgery* **6** 697, 1939.

32 Van Liere, E. J., and Sleeth, C. K. The Emptying Time of the Normal Human Stomach as Influenced by Acid and Alkali with a Review of the Literature, *Am J Digest Dis* **7** 118, 1940.

with stimulation of the gastric secretion by the alkali, and (3) a direct effect on the gastric musculature. None of these theoretic explanations is entirely satisfactory.

Using a somewhat similar method, Reynolds and his associates³³ studied the gastrointestinal response of children to test meals consisting of various types of milk to which had been added barium sulfate. The 7 healthy children included in this study had been observed previously in an acid-base, mineral balance study covering more than seven months, and all gastrointestinal motility patterns were already known. Roentgen examinations were made frequently over a period of seventy-two hours. The soft curd milks (evaporated and base exchanged) left the stomach in much less time than did pasteurized milk and appeared to have a more orderly progression throughout the entire alimentary canal. Subsequent studies were made,³⁴ comparing the rate of emptying in water, milk, cream, meat and carbohydrate mediums. In this study over 300 exposures illustrated variations among individual responses to the same meal and different meals and in the response of different sections of the alimentary canal. The water meal produced the most consistent and constant reactions in both the stomach and the intestine, and the milk, cream and carbohydrate meals were all subject to an initial delay in gastric emptying, the greatest retardation following the intake of cream. The meat meals, containing 7 per cent protein and 3.5 per cent fat, produced less delay in gastric emptying than that caused by cream and made more rapid progress through the small intestine until the terminal portion of the ileum was reached. At this point the protein-fat mixtures seemed to exert a stronger motor inhibition than did the cream mediums. After the initial delay in gastric emptying, the carbohydrate meal filled the entire small intestine very rapidly, and at the same time the stomach increased in size, indicating the extreme rapidity of action of a mechanism tending to bring the contents of the stomach to isotonicity by osmotic induction of water into it. None of these data are surprising or distinctly new, but they offer an interesting confirmation of views previously held.

The effect of products of protein hydrolysis in inhibiting gastric motility was studied by Thomas and Crider.³⁵ These authors introduced

33 Reynolds, L., Macy, I. G., and Souders, H. J. The Gastrointestinal Response of Children to Test Meals of Barium and Pasteurized, Evaporated, and Base-Exchanged Milks, *J. Pediatr.* **15** 1, 1939.

34 Reynolds, L., Macy, I. G., Hunscher, H., and Olson, M. B. The Gastrointestinal Response of Average, Healthy Children to Test Meals of Barium in Milk, Cream, Meat and Carbohydrate Media, *Am. J. Roentgenol.* **43** 517, 1940.

35 Thomas, J. E., and Crider, J. O. Inhibition of Gastric Motility Associated with the Presence of Products of Protein Hydrolysis in the Upper Small Intestine, *Am. J. Physiol.* **126** 28, 1939.

numerous materials resulting from commercial or in vivo hydrolysis of proteins into the small bowel. All of the substances except the amino acid mixtures caused inhibition of gastric motility within fifteen seconds, in a manner comparable to the effect of hydrochloric acid. Bilateral vagotomy prevented the occurrence of such an inhibition on gastric motility, and the authors conclude that the products of protein hydrolysis produce inhibition of gastric motility by acting in the intestine as stimuli for the enterogastric reflex.

Heinin²⁵ studied the gastric emptying time of dogs under conditions of vitamin A deficiency. For one half of the animals the final gastric emptying time was increased appreciably, but in the remainder of the group of experimental animals there was no significant deviation from the normal. The variability of the results as regards the effect of avitaminosis A on gastric emptying time was thought to be due to changes in the central nervous system rather than in the alimentary tract.

Further evidence of the influence of hypothalamic stimulation on gastric motility is presented by Wang and his associates³⁶. They made direct observations on more than 50 animals (cats) by a faradic stimulation with light anesthesia of the hypothalamic area. The effects of such stimulation on the gastrointestinal tract were visualized by means of a transparent window or recorded by the balloon method. Stimulation of the hypothalamus anterior to the infundibular region caused immediate blanching and occasional inhibition followed by a marked excitatory response. The onset of the latter was slow and gradual, and its effect lasted for several minutes. Section of both vagus nerves did not abolish this effect. Vagal effects were obtained when the hypothalamus at or behind the infundibular level was stimulated. Such a response could be elicited in chronic spinal cats and was abolished after bilateral vagotomy.

Further studies on the absorption of dextrose solutions by the stomach were made by Shay and his collaborators³⁷. Contrary to most previous studies but in accordance with some other recent ones, these authors found that considerable amounts of dextrose may be absorbed by the stomach alone when the solutions are of high concentration. From dextrose concentrations below 15 per cent no appreciable absorption could be demonstrated. Studies on absorption and dilution by the

36 Wang, S. C., Clark, G., Dey, F. L., and Ranson, S. W. Further Study on the Gastro-Intestinal Motility Following Stimulation of the Hypothalamus, *Am J Physiol* **130** 81, 1940.

37 Shay, H., Gershon-Cohen, J., Fels, S. S., and Munro, F. L. The Absorption and Dilution of Glucose Solutions in the Human Stomach and Duodenum, *Am J Digest Dis* **6** 535, 1939.

duodenum as contrasted with the stomach were made possible by the use of a multilumen tube. It was demonstrated that as a diluting organ the importance of the stomach is much less than that of the duodenum, the latter showing remarkable powers in changing from an organ of dextrose absorption to one of dextrose dilution. The best absorption of dextrose from the duodenum was usually noted in solutions at or near isotonicity. With hypertonic solutions the duodenum is capable of mobilizing enormous quantities of fluid in short periods, and the greater the concentration above isotonicity, the greater will be the dilution and correspondingly, the less the actual absorption. There appears to be a reciprocal shift of chloride to dextrose concentration in the duodenum in the attempt to maintain isotonicity. It is of incidental interest that Shay and his co-workers³⁸ carried out studies also on the absorption of hydrochloric acid in the human stomach. They were unable to demonstrate any absorption, even from solutions in a concentration of 1 per cent. With this concentration gastric secretion was obviously completely inhibited.

Cannulation of gastric and duodenal fistulas in dogs provided the basis for observations on estimations of gastric and duodenal p_H experiments carried out by Thomas.³⁹ It was found that under conditions designed to produce the maximal normal acidity in the intestinal contents during digestion the acidity in the duodenum near the pylorus rarely exceeded a p_H of 3 and was generally near a p_H of 4. The acidity was less in other parts of the duodenum and in the upper part of the jejunum. The contents of the pyloric antrum near the pylorus, as could have been predicted, were consistently less acid than the contents of the body of the stomach, a reaction usually between a p_H of 2 and 3. The authors suggest that the "receptive relaxation" of the duodenum, by causing accumulation of the duodenal contents in the vicinity of the pylorus at the moment of exit of gastric contents, facilitates quick dilution and partial neutralization of the chyme. It is obvious, however, that dilution can be quickly accomplished by the rapid outpouring of fluid in the presence of hypertonic solutions, as has already been noted by Shay and others.

An unusual finding is that reported by Herrin⁴⁰ on the secretion of ammonia in the succus entericus obtained from a Thiry-Vella loop of jejunum in the dog. The concentration of ammonia in the juice was

38 Shay, H., Gershon-Cohen, J., and Fels, S. S. The Absorption of Hydrochloric Acid by the Human Stomach, *Am J Digest Dis* **6** 361, 1939.

39 Thomas, J. E. The Maximal Acidity of the Intestinal Contents During Digestion, *Am J Digest Dis* **7** 195, 1940.

40 Herrin, R. C. The Secretion of Ammonia by the Small Intestine of the Dog, *Am J Physiol* **129** 146, 1940.

influenced by a number of factors. It could be increased by giving a high protein diet and diminished by changing to a diet high in carbohydrate. The ammonia content of the jejunal secretion paralleled changes in the urinary excretion of nitrogen. Intravenous injection of certain amino acids resulted in a marked increase in the ammonia content of the juice, as did injection of insulin. The author interpreted his observations by assuming that the ammonia was secreted by the glands of the jejunum. Its concentration in the juice appeared to be determined largely by the protein metabolism of the gland cells, it apparently served no physiologic purpose as far as digestion was concerned, and it appeared in the juice and the blood from the intestine because of its easy diffusibility.

New and ingenious methods of study have permitted renewed investigations of the mechanism of the motor activity of the gastrointestinal tract that are worthy of notice. Weltz,⁴¹ by the use of plane-kymograms, has made a series of fluoroscopic observations on the motor activity of the entire gastrointestinal tract. What he interprets as evidence of tonus in the stomach is apparently the factor controlling peristalsis. With a low degree of tonus, peristalsis frequently becomes quiescent, with the increase of tonus, peristalsis starts suddenly, but if tonus again decreases, peristalsis may cease. The starting of gastric peristalsis after filling of the stomach may be the result of the stretching stimulus, but this of necessity must diminish with progressive emptying of the organ, and peristaltic emptying of the last traces of gastric contents cannot be explained by the stimulus of distention. The complete emptying of the stomach can be understood only by assuming a steady increase in tonicity during the act. In the presence of pyloric stenosis due to carcinoma, irregular cufflike contractions and spasm of the antrum may occur instead of normal peristalsis, and they are similar in appearance to the contractions noted in the first stage of vomiting. In the small bowel the author noted peristaltic waves and, in addition, a second kind of propulsive movement, which occurred especially if large quantities of gastric contents were suddenly emptied into the intestine. A similar picture is noted in the presence of pyloric insufficiency and in the stomach after an operation. The usual picture of colonic movement is one of slight restlessness of the haustra, with frequent increases in haustral activity in a single segment. Stomach-like peristalsis was observed in the middle of the transverse colon in the presence of partial obstruction. Complete obstruction of the colon was associated with repeated cufflike contractions similar to those noted in the region of the pylorus in the presence of obstruction.

41 Weltz, G. A. Motility of the Gastro-Intestinal Tract in Man as Observed in Plane-kymograms, *Radiology* **33** 462, 1939.

An entirely different approach was that made by Bozler,⁴² who carried out electrophysiologic studies on the action potentials of the stomach and small intestine in animals. Muscle contractions were accompanied by a repetitive discharge and were, therefore, analogous to a tetanic contraction of skeletal muscle. The frequency of discharge ranged from about 1 per second during gastric peristalsis to 10 per second during a peristaltic rush in the small intestine. Grading of the contractions was made possible by noting the variation in the number and frequency of impulses. The size of the impulses varied with the strength of the contractions, probably because only part of the musculature was active during weak contractions. The peristalsis in the small intestine of the cat and dog appeared to consist of rhythmic contractions on the oral side of a bolus, whereas the peristaltic rush in the rabbit was a continuous wave of contraction.

Douglas and Mann,⁴³ using exteriorized loops of small intestine at different levels, noted the occurrence and rate of rhythmic contractions in dogs. Rhythmic contractions were found to be a relatively rare form of movement in these preparations, but their rate was practically a constant for any given loop. The rate for any given loop was found to be a function of its distance from the pylorus, the loop at the highest level having the highest rate and that at the lowest level a correspondingly lower one. The rate was not affected by fasting, feeding or sleep, except that in recently fed animals rhythmic contractions were less commonly observed than in fasting animals. Degenerative vagal and splanchnic section did not affect the rate of these contractions. These investigators also studied the activity of exteriorized loops of the lower part of the ileum in continuity in relation to the ingestion of food. A regular cycle of activity was noted in the normal animal, namely, a rapid motor response to feeding followed by prolonged activity which gradually diminished until, after forty-eight hours of fasting, the activity was extremely feeble. The motor response was noted as constant after feeding by gastric fistula, as in the normal animal, and was not affected by double vagotomy at the level of the thorax. Partial interruption of continuity by a short-circuiting operation caused inconstant results, but complete isolation of the loop resulted in absence of the motor response to feeding and complete dissociation of the activity of the loop from ingestion of food. The authors take this evidence to indicate that the degree and type of activity at the lower portion of the ileum in the dog

42 Bozler, E. Electrophysiological Studies on the Motility of the Gastro-Intestinal Tract, *Am J Physiol* **127** 301, 1939.

43 Douglas, D. M., and Mann, F. C. An Experimental Study of the Rhythmic Contractions in the Small Intestine of the Dog, *Am J Digest Dis* **6** 318, 1939, The Activity of the Lower Part of the Ileum of the Dog in Relation to the Ingestion of Food, *ibid* **6** 434, 1939.

is intimately connected with the ingestion of food, that the so-called gastroileac reflex is not merely a feeding reflex but depends for its mediation on the continuity of the intestine, and, finally, that the vagus nerves, which are generally believed to be the motor nerves of the small bowel, play little part in its mediation

More complete experiments were carried out,⁴⁴ in which loops of jejunum, ileum and colon were exteriorized in continuity, and further studies were made on the so-called gastroileac reflex in relation to feeding. A prompt motor response following feeding was noted in both the jejunal and the ileac loops, occurring more rapidly in the jejunal loops than in the ileac. Moreover, in an animal in which two exteriorized loops of small intestine at different levels were prepared, the motor response constantly appeared in the loop at the higher level before appearing in the lower loop, a finding entirely in keeping with the observations of Bozler, to which reference has already been made, and with previous studies, including those of Alvarez on intestinal gradients. Feeding by duodenal fistula gave as constant results as oral feeding, and section of the intestine oral to the loop and reanastomosed in such a way as to prevent union of the muscular coats and the intrinsic enteric plexuses did not prevent occurrence of the motor response. A constant motor response after feeding was noted in the distal part of the colon but not in the proximal part. These findings suggest that after ingestion of food a wave of activity traveling at the rate of about 1 cm per second passes down the length of the small intestine. The gastriocolic reflex does not appear to be a part of this excitation, and the authors suggested that the term "gastroileac reflex" is not sufficiently inclusive.

By means of cinematography, Barclay⁴⁵ observed the movements of the terminal portion of the ileum and the action of the ileocecal "valve." Activity in this region was stimulated by the intake of food. Two main types of contraction were noted—a propulsive or rapid rush movement, and a churning, slow nonpropulsive movement. In the records obtained the ileocecal "valve" did not appear to act in a valvular manner to prevent the passage of food. Although capable of contraction, it was seen in some of the records to be wide open and empty and in others to be wide open and full, with no sign of narrowing. There was no indication that ileal contents were pressed up against it as at the pylorus. The author gained the impression that normally at this region it exerts little influence on the passage of food. He believes, however, that in the presence of local inflammatory condi-

44 Douglas, D. M., and Mann, F. C. The Gastro-Ileac Reflex. Further Experimental Observations, *Am J Digest Dis* 7: 53, 1940.

45 Barclay, A. E. Intestinal Movements in the Ileocecal Region, *Radiology* 33: 170, 1939.

tions it may exert a valvular action, as indicated by the delay noted in this region in disease of the appendix

Bargen, Wesson and Jackman⁴⁶ contributed an embryologic review and anatomic study of the musculature, blood and lymphatic supply of the ileocecal junction of man. They believe it has been demonstrated in man that the circular and longitudinal muscles of both the ileum and the colon enter the labia of the ileocecal junction and comprise a structure with sphincteric action. Observations in 2 patients on the results of stimulation of this region, with resulting contraction and relaxation, suggest to the authors that its function is concerned with the production of a barrier between the ileum and the colon when such a barrier is needed. They also suggest that the demonstration of a lymphatic block at the tip of the labia of the ileocecal junction is of some clinical interest, as it may help to explain the limitation of cancerous growths of the ileocecal junction to the cecal side as well as the fact that melanosis coli does not advance proximally beyond this region.

Kleitsch and Puestow⁴⁷ noted the effect of intravenous solutions commonly used in surgical practice and of insulin on the peristaltic rate and tonus in isolated intestinal transplants. Physiologic sodium chloride solution administered by drip venoclysis produced a definite increase in the rate and strength of the contractions, whereas 10 per cent dextrose solution had little, if any, effect on motility of the small bowel. Insulin caused a progressive diminution in peristaltic rate and strength and in intestinal tonus when administered alone or combined with a solution of dextrose.

Brandberg⁴⁸ presents an interesting experimental study on intestinal motility in mechanical ileus. Observations were made on rabbits in which obstruction by obturation or strangulation was established at different levels in the intestinal tract. The results were studied by the abdominal window method and confirmed the view that in mechanical ileus there first sets in a stage of increased motility in the intestine above the obstruction, followed by a stage of paralysis due undoubtedly to distention of the bowel and impaired circulation of the blood. The stage of increased motility varies greatly in duration with the situation of the obstruction. With obstruction of the upper part of the small intestine this stage is short, and distention and paresis rapidly set in. The lower the obstruction is situated, the more favorable are the con-

46 Bargen, J. A., Wesson, H. R., and Jackman, R. J. Studies on the Ileocecal Junction (Ileocecus), *Surg., Gynec. & Obst.* **71** 33, 1940.

47 Kleitsch, W. P., and Puestow, C. B. Studies of Intestinal Motility. The Effect of Intravenous Solutions and of Insulin upon Peristalsis, *Surgery* **6** 679, 1939.

48 Brandberg, R. An Experimental Study of Intestinal Motility in Mechanical Ileus, *Acta chir. Scandinav.* **83** 287, 1939.

ditions, and in consequence a long period of increased bowel movements occurs, especially in cases of obstruction of the distal portion of the colon, paresis setting in only gradually and then not completely. The earlier view that in cases of obstruction by strangulation the motility in the parts of the intestine above the obstruction is initially less lively than in cases of obstruction by obturation did not prove to be correct. Although these results are not surprising, the fact that they offer accurate visualization and confirmation of clinical impressions makes them of practical value.

Absorption of various material from the small bowel continues to offer an excellent opportunity for investigative work and has a practical bearing on various therapeutic problems. One study of real interest is that reported by Dennis and Visscher⁴⁹ on the influence of various factors on intestinal absorption involving osmotic work in the dog. Active absorption against large concentration gradients occurs from the lower part of the ileum of the trained unanesthetized dog. Thirty-Vella loops from the upper, middle and lower portions of the ileum, in the order named, show progressively more rapid absorption. Of especial interest is the fact that true excitement was found to be associated with a diminished absorption rate. Anesthetization of excitable dogs increased the rate of active absorption, whereas anesthetization of placid dogs caused no such change. Excitement caused blanching of the ileal mucosa, suggesting the observations previously alluded to on blanching of the bowel following hypothalamic stimulation. The rate of active absorption is faster in chronic loop experiments than in acute experiments. Ingestion of food does not alter absorption rates outside the limits of normal variability.

Van Liere and Vaughan⁵⁰ report experiments confirming the statement that chloride ion is absorbed from the intestine against a diffusion gradient in the presence of a polyvalent anion (sulfate). This absorption of chloride against a diffusion gradient is reduced but not prevented by anoxia, which, however, has no effect on the absorption of sodium chloride from the mammalian small intestine.

An interesting abnormality of intestinal absorption is that studied by Dennis and Wood⁵¹ in adrenalectomized dogs. The animals were maintained on high sodium, high bicarbonate, low potassium diets after

49 Dennis, C, and Visscher, M. B. The Influence of Various Factors upon Intestinal Absorption Involving Osmotic Work in the Unanesthetized Dog, *Am J Physiol* **129** 176, 1940.

50 Van Liere, E. J., and Vaughan, P. E. The Influence of Anoxia on the Absorption of Sodium Chloride and Sodium Sulphate from the Small Intestine, *Am J Physiol* **129** 618, 1940.

51 Dennis, C, and Wood, E. H. Intestinal Absorption in the Adrenalectomized Dog, *Am J Physiol* **129** 182, 1940.

the withdrawal of the adrenal cortical hormone. In such a condition, there was a marked decrease in the rate of absorption of sodium, potassium and chloride from the ileum, a situation that was reversed in every case by the administration of an extract of adrenal cortex. When the cortical extract was withdrawn, the rate of sodium absorption in general declined more than that of potassium absorption, and at times there seemed to be an actual reversal in the direction of sodium, which was sometimes excreted into the intestine in relatively large quantities, although potassium was still being absorbed. In spite of essentially normal blood chemistry and objectively excellent health, the behavior of the intestine in the adrenalectomized dog could not be maintained in the absence of adrenal cortical hormone.

The effect of another endocrine secretion on intestinal function was studied by Althausen, Keir and Stockholm,⁵² who report further experiments on the calcium exchange of the intestine in the presence of experimental hyperthyroidism. They showed that administration of thyroxine, of subpurgative doses of castor oil or of cascara practically doubled the fecal output of calcium in rats. Restriction of the food intake or administration of morphine markedly decreased the excretion of calcium in hyperthyroid rats. The authors, therefore, conclude that hyperperistalsis and overeating are the chief causes of increased fecal output of calcium in hyperthyroid rats maintained on a calcium-free diet. They noted no appreciable change in calcium absorption in the presence of hyperthyroidism.

Absorption of iron from the gastrointestinal tract was studied by Moore and his collaborators.⁵³ Owing to the fact that serum iron has been demonstrated to be transport iron, a new approach to the study of absorption of iron from the gastrointestinal tract was available, although the measure of serum iron reflected the fact and degree of absorption rather than the total amount. From the data available in the literature and those acquired in this investigation, the following picture of iron absorption was constructed. When ingested iron reaches the stomach, it is subjected to the influences of the prevailing acidity, the free gastric hydrochloric acid apparently having two functions, first, to ionize and dissolve iron not already present in solution or not in an ionized state and, second, to delay the formation of insoluble and undissociated iron compounds. Since these form at a p_H above 5, some change would appear to occur in the stomach of patients with achlorhydria. Iron delivered into the duodenum is subjected to two influences,

52 Althausen, T. L., Kerr, W. J., and Stockholm, M. Calcium Exchange of the Intestine in Experimental Hyperthyroidism, *J. Clin. Investigation* **18** 763 1939.

53 Moore, C. V., Arrowsmith, W. R., Welch, J., and Minnich, V. Studies in Iron Transportation and Metabolism. Observations on Absorption of Iron from the Gastrointestinal Tract *J. Clin. Investigation* **18** 553, 1939.

the alkaline intestinal juices and certain reducing agents, the latter tending to reduce any trivalent iron to the ferrous form before the change to nonionizable salts has occurred. Iron is absorbed from the intestinal tract largely, if not entirely, as ferrous iron. The degree to which ferrous salts are assimilated would seem to depend on the capacity of the intestinal contents to reduce them. It is the consensus that absorption takes place largely in the upper portion of the small bowel, where the iron passes directly into the blood plasma and not to any extent into the intestinal lymph channels. The influence of achlorhydria and an abnormally increased intestinal rate on hemopoiesis is obvious with such a hypothesis.

Experiments by Hahn and his collaborators⁵⁴ on the fate of iron excreted in the urine, bile and feces of dogs given radioactive iron by vein are of interest. Except for a small initial excretion for a few days in the urine and feces, little of the iron administered was lost. The body controls its iron stores by absorption or lack of it rather than by the capacity to eliminate it. The authors consider that the evidence is overwhelming that the dog excretes iron with difficulty and in small amounts by means of the biliary and gastrointestinal tracts.

Further observations on the impairment of intestinal absorption in deficiency diseases are contributed by Erf and Rhoads,⁵⁵ who studied the absorption of aminoacetic acid from the gastrointestinal tract in patients with untreated sprue and pernicious anemia. In these patients aminoacetic acid appeared to be absorbed more slowly than was normal, although this abnormality was corrected by adequate liver therapy. Evidence of malabsorption was not demonstrable in patients with intractable diarrhea, severe refractory anemia or pernicious anemia in complete or partial remission. Curiously enough, however, the authors demonstrated poor absorption of this substance in 2 patients with cirrhosis of the liver.

An interesting therapeutic suggestion is found in the report of Curtis and Ballmer,⁵⁶ who apparently demonstrated that plain liquid petrolatum and two emulsified preparations of petrolatum and agar removed appreciable amounts of carotene from ingested food. Plain liquid petrolatum saturated at room temperature with carotene still removed carotene from ingested food, but in lesser amounts, whereas apparently saturation of liquid petrolatum with carotene at body temperature prevented any interference with absorption of this precursor of vitamin A.

54 Hahn, P. F., Bale, W. F., Hettig, R. A., Kamen, M. D., and Whipple, G. H. Radioactive Iron and Its Excretion in Urine, Bile and Feces, *J. Exper. Med.* **70** 443, 1939.

55 Erf, L. A., and Rhoads, C. P. The Glycine Tolerance Test in Sprue and Pernicious Anemia, *J. Clin. Investigation* **19** 409, 1940.

56 Curtis, A. C., and Ballmer, R. S. The Prevention of Carotene Absorption by Liquid Petrolatum, *J. A. M. A.* **113** 1785 (Nov. 11) 1939.

Previous suggestions that the duodenum exerts a hormonal control of carbohydrate metabolism are apparently disproved by Loew, Gray and Ivy⁵⁷ These investigators employed various preparations of pancreas-free extracts of intestinal mucosa and failed to demonstrate in unanesthetized dogs any effect on the level of blood sugar

Secretion by the colonic mucosa has been studied by Wright, Florey and Jennings,⁵⁸ who have demonstrated that parasympathetic stimulation either by faradic current or by cholinergic drugs caused the appearance of a strongly alkaline fluid It contained a proteolytic enzyme, chlorine and phosphate ions and appreciable amounts of calcium Sympathetic stimulation did not excite any secretion Narcotics greatly diminished the rate of secretion, and atropine inhibited it completely The resting or atropinized animal has the ability to reabsorb this secretion completely

An interesting effect of distention of the colon and stimulation of its nerve supply has been observed by Goldman and Ivy,⁵⁹ who demonstrated in dogs and monkeys that distention caused an inhibition in the flow of bile from the liver in the absence of active choleresis stimulated by bile acids A similar response was noted following stimulation of the central end of the colonic, inferior mesenteric, superior mesenteric and pelvic nerves, indicating that this inhibition is of reflex origin, while section of the hepatic nerves prevented the aforementioned effects and actually was followed by an increase in bile flow

Some new information and a good deal of confirmation of previous experimental and clinical findings are supplied by the experiments of Coffey, Mann and Bollman,⁶⁰ who studied the digestion and absorption of fat, protein and carbohydrate in the normal dog Control experiments on standard diets, high carbohydrate, high protein and high fat diets were performed, with a careful analysis of the fecal residue It was found that normal dogs utilize foodstuffs efficiently The fecal excretion of fat varied from 2.1 to 4 per cent, most of which was fatty acids The fecal nitrogen was found to be fairly constant in absolute amount, except for a variation roughly proportional to the bulk of the feces When

57 Loew, E. R., Gray, J. S., and Ivy, A. C. Is a Duodenal Hormone Involved in Carbohydrate Metabolism? *Am J Physiol* **129** 659, 1940

58 Wright, R. D., Florey, H. W., and Jennings, M. A. The Secretion of the Colon of the Cat, *Quart J Exper Physiol* **28** 207, 1938

59 Goldman, L., and Ivy, A. C. The Effect of Distention of the Colon and Stimulation of Its Nerve Supply on the Flow of Bile from the Liver, *Ann Surg* **110** 755, 1939

60 Coffey, R. J., Mann, F. C., and Bollman, J. L. I Fecal Residue of Fat, Protein and Carbohydrate in the Normal Dog, *Am J Digest Dis* **7** 141, 1940, II The Effect of the Exclusion of Bile on the Absorption of Foodstuffs, *ibid* **7** 143, 1940, III The Influence of the Pancreas on the Utilization of Foodstuffs, *ibid* **7** 144, 1940, IV Substitution Therapy in Experimental Pancreatic Deficiency, *ibid* **7** 149, 1940

calculated as percentage of the protein of the diets used, the fecal nitrogen increased as the amount of dietary protein decreased. With low protein diets as much as 50 per cent of the nitrogen intake may be excreted in the feces. Carbohydrate excretion in the feces was only slightly affected by the diet, varying from 1 to 3 per cent. The exclusion of bile from the duodenum by an operative procedure, with resultant obstructive jaundice, still permitted utilization of over 50 per cent of large and moderate amounts of ingested fat. The feeding of a low fat, high protein diet was accompanied by utilization of over 70 per cent of the ingested fat. Only with a diet low in fat was there a preponderance of neutral fat in the feces. Nitrogen excretion under these conditions was definitely increased, and the recovery in the feces of 180 per cent of what was originally contained in a high fat diet offers striking evidence of loss of nitrogen from the intestinal canal, which appears to be proportional to the bulk of the feces and independent of the protein content of the diet. Utilization of carbohydrate was unaffected by the absence of bile. Pancreatectomy or the production of a complete pancreatic fistula resulted in an immediate loss of utilization of fat and carbohydrate, and an increased excretion of fecal nitrogen was noted, which was related to the increased bulk of the feces. It was less when diets rich in protein were employed. Evulsion of the pancreatic ducts was followed by a much more gradual failure of food utilization and appeared to parallel the degenerative changes occurring in the acinar tissue of the pancreas. Incomplete pancreatic fistulas or incomplete evulsion of the pancreatic ducts produced no detectable alteration of food utilization and indicated that only very small amounts of external pancreatic secretion are necessary to maintain complete digestion. Replacement therapy definitely reduced the loss of carbohydrate in the feces when large amounts of carbohydrate were included in the diet. Pancreatic juice, raw pancreas or pancreatin was effective, but only when given in very large amounts. Concomitantly with the improvement of carbohydrate utilization, the bulk of the feces was decreased and the amount of nitrogen reduced, but there seemed to be no direct effect of the replacement therapy on the amount of fecal nitrogen. In some experiments it appeared that slight improvement in fat utilization occurred when carbohydrate utilization was nearly at normal levels as the result of replacement treatment. The failure of replacement therapy was in marked contrast to normal utilization of foodstuffs when but small amounts of pancreatic juice drain into the intestine, as in animals with incomplete fistulas.

Numerous investigations have been made of the physiologic effects of various drugs on the alimentary tract and for the most part are in agreement. Because of the widespread clinical use of most of these preparations, it is thought advisable to review briefly the results of these pharmacologic studies. Although certain of the investigative findings

are by no means new, they offer confirmation of previous work, and inspection of the entire group of drugs may prove of interest and value. This is particularly true, for example, as drugs commonly employed in the preoperative and postoperative care of patients have either a strong motor or a strong inhibitory influence on the tone and on the peristaltic activity of the gastrointestinal tract. Anesthetic agents undoubtedly are in part responsible for some of the late, as well as the immediate, postoperative symptoms—nausea, vomiting, distention and gas pains.

Bisgard and Johnson,⁶¹ like others, showed that the administration of morphine sulfate to man caused a marked increase in tonus in both the stomach and the small bowel. In the stomach there was an increase in the frequency and amplitude of peristaltic contractions, but in the small bowel a diminution of their amplitude was observed. In dogs, simultaneous observations were made on the stomach, the ileum and the colon and showed that there was an immediate increase in gastric tone and muscular activity, which persisted for about two hours. Gastric contractions greatly diminished in both frequency and amplitude for as long as six hours. Both the small bowel and the colon showed similar effects, namely, increased tone and diminishing motor activity, but in both there was an early return to normal. Myers⁶² studied the effect of morphine sulfate, diacetylmorphine and some related alkaloids in cats. The majority of the experiments showed a decrease in tone and in frequency and amplitude of movements of the digestive tract, although some animals showed an increase in gastric tone and activity following the use of morphine. Codeine sulfate produced variable results at times a reduction and in other instances a slight increase in gastric tone and amplitude of movements being noted, but these were slight and short lived as compared with those produced by morphine or by diacetylmorphine (heroin). The effects of dilaudid hydrochloride on the stomach were far from constant, most animals showing an immediate relaxation of the stomach, with a decrease in the amplitude of the movements. The effects of dihydrocodeinone bitartrate (dicodid) on the stomach resembled those of codeine and consisted in a small, gradual increase in tone, followed by a relaxation to a subnormal level. Eukodol (dihydro-oxycodone) produced somewhat similar effects. All of the aforementioned drugs appeared to produce constant effects on the pyloric sphincter, namely, an increase in the tone of the sphincter accompanied

61 Bisgard, J. D., and Johnson, E. K. The Influence of Certain Drugs and Anesthetics upon Gastrointestinal Tone and Motility, *Ann. Surg.* **110** 802, 1939.

62 Myers, G. N. The Effects of Morphine, Diacetylmorphine and Some Related Alkaloids upon the Alimentary Tract. I. Stomach and Pylorus, *J. Hyg.* **39** 375, 1939, II. Small Intestine and Ileo-Colic Sphincter, *ibid.* **39** 391, 1939, III. Cecum and Colon, *ibid.* **39** 512, 1939.

with an increase in the amplitude of rhythmic movements. Dilaudid hydrochloride appears to be approximately eight times more active than morphine on the pylorus, while diacetylmorphine (heroin) is about one and a half times more potent than morphine. The effects of these three drugs last several hours, in contrast to the effects of codeine, dihydrocodeinone bitartrate (dicodid) and dihydro-oxycodone hydrochloride (eukodol), which are of short duration and slight degree. On the small intestine the effects of morphine were similar to those mentioned, namely, increased tone and peristaltic movements. Similar effects were noted after the use of dihydrocodeinone, codeine and dihydro-oxycodone, but in diminishing degrees. Morphine appeared to increase the tonus and movements of the ileocolic sphincter. Reagan and Puestow,⁶³ investigating by direct observation the motility of isolated segments of a dog's colon, produced evidence that morphine increases the tonus, frequency and strength of colonic contractions. The observation of diminishing effects of morphine and related alkaloids on the lower levels of the gastrointestinal tract is in agreement with the work of most previous investigators.

Seconal (sodium propylmethylcarbonylallylbarbiturate) was found by Bisgard to have no effect on the motor activity of the dog's stomach but was markedly inhibitory to the ileum and colon. The tone in both the small and the large bowel was markedly reduced, and muscular activity of the large bowel was almost entirely abolished, although the ileum continued to contract with normal frequency. The results of administration of evipal (C-C-cyclohexenyl-N-methyl-barbituric acid) were observed by the same author in man and in dogs. Evipal administered intravenously to man caused an immediate reduction in gastric tone and, with complete loss of consciousness, total abolition of motor activity, which returned promptly as complete consciousness was regained (after approximately thirty minutes). In the dog similar effects were noted, except that in the ileum rhythmic contractions continued with diminished amplitude although peristalsis was abolished. The action of atropine sulfate was noted by Bisgard in man and in dogs. After subcutaneous administration in man, there was a marked diminution of tone and of frequency and amplitude of contractions for approximately one and a half hours in both the stomach and the small bowel. For about thirty minutes peristalsis was entirely abolished in the ileum. In the dog the drug caused only relaxation and diminution of activity in the colon. When it was combined with morphine the two drugs counteracted each other,

63 Reagan, R. E., and Puestow, C. B. The Activity of Isolated Segments of the Colon of Dogs, with Special Reference to the Influence of Certain Drugs, *Surgery* 6: 663, 1939.

so that the motor effect of morphine and the inhibitory effect of atropine resulted in essentially no demonstrable effect on gastric motility. Myers, in experiments on cats, noted that atropine modified the effects of morphine by producing a decrease in the tone and movements of the small bowel for varying periods, but subsequent injections of morphine during the period of atropine inhibition produced a further increase in tone and motility. He also noted that atropine abolished the effects of morphine and its related alkaloids on the tone and peristaltic movements of the cecum and colon, although according to Reagan the drug had little, if any, effect on colonic motility when observation was made on isolated segments of the colon. During intubation studies of the small intestine and the colon combined with fluoroscopic study of human subjects, Elsom and Drossner⁶⁴ also observed definite and prolonged effects on the small bowel and colon following therapeutic doses of atropine and belladonna. These effects consisted in a marked decrease in tone and peristaltic activity and a less striking effect on rhythmic contractions. This is entirely in keeping with clinical observations but is at variance with the work of some previous investigators.

The effect of syntropan (the phosphate of 3-diethylamino-2,2-dimethylpropylester of tropic acid), one of the newer antispasmodics, was studied by Clark and his collaborators⁶⁵. In unanesthetized dogs intramuscular administration of the drug produced relaxation of gastric tone and inhibition of peristaltic activity, but only a weak inhibition of gastric secretion excited either by histamine or by meat was observed as compared to that obtained by the use of atropine. Duodenal motor activity was depressed, with less effect on the heart rate, size of the pupils and salivation than followed the use of atropine. The effect on excised segments of small intestine from rabbits and cats depended on the dose employed. In small amounts it effectively antagonized the stimulation produced by cholinergic drugs without muscular depression, but large amounts produced actual muscular depression. About one hundred times more syntropan than atropine was required to produce the same degree of depression of the intestine. In the unanesthetized dog syntropan antagonized the stimulating effect of acetylbetamethylcholine (mécholyl), morphine and pitressin to a far greater extent than did an equivalent dose of atropine, when the drug was administered by the intramuscular route. The effect of trasentin (diphenylacetyldiethylaminoethanol

64 Elsom, K. A., and Drossner, J. L. Intubation Studies of the Human Small Intestine. The Effect of Atropine and Belladonna on the Motor Activity of the Small Intestine and Colon, *Am J Digest Dis* 6: 589, 1939.

65 Clark, B. B., Shires, E. B. S., Jr., Campbell, E. H., and Welch, C. S. The Action of Syntropan on the Gastrointestinal Tract, *J Pharmacol & Exper Therap* 66: 464, 1939.

hydrochloride), another synthetic substitute for atropine, was observed by Necheles and his associates⁶⁶ In the unanesthetized dog intramuscular administration of the drug in effective doses abolished or diminished gastric hunger contractions In anesthetized dogs it diminished or abolished the muscular spasm and contractions of the stomach and of the small and the large bowel produced by various drugs or by vagal stimulation Clinical trial of the drug by Spier, Neuwelt and Necheles⁶⁷ afforded some evidence that it offers occasional relief to patients suffering from ulcer or an irritable colon when orthodox therapy fails Three patients with symptoms due to hypertrophic gastritis, unrelieved by other forms of therapy, received complete relief after use of the drug, and it controlled postoperative diarrhea in 5 patients previously refractory to usual medication (except camphorated tincture of opium) The authors concluded that the drug has a definite antispasmodic effect, clinical as well as experimental, its action on the small bowel probably being dependent on slowing down of intestinal motility and lowering of tonus, with restitution of a more normal intestinal gradient Bisgard and Johnson, like other observers, found that glyceryl trinitrate administered sublingually produced in man and dogs a striking diminution of tone and peristaltic activity in the stomach and in the ileum Complete abolition of parasympathetic activity was not obtained, the effect of the drug lasting approximately twenty minutes In 2 patients, hunger contractions previously induced by the administration of dilute hydrochloric acid were abolished by glyceryl trinitrate

Histamine given intravenously to anesthetized dogs with Thiry-Vella fistulas was found by Wolff⁶⁸ to cause a depression of gastrointestinal tone and motility This is distinctly at variance with preceding observations, in which a definite increase in tone and motility and in unanesthetized dogs a complete lack of any effect have been noted by some observers Acetylcholine, on the contrary, produced a definite increase in tonus and motility of the gastrointestinal tract, although here again Wolff's findings are in disagreement with several previous observations Wolff's observations on the results of administration of acetylcholine are in keeping with those of most observers and are confirmed by the work of Necheles and Masur, who also showed that constant intravenous injection of small amounts of acetylcholine in dogs is followed by a

66 Necheles, H , Neuwelt, F , Steiner, N , and Motel, W G The Study of a New Spasmolytic Drug Diphenylacetyl-diethylaminoethanol-Hydrochloride (Trasentin), *Am J Digest Dis* 6 39, 1939

67 Spier, E , Neuwelt, F , and Necheles, H Clinical Study of New Synthetic Spasmolytic Drugs Diphenylacetyl-diethylaminoethanol, *Am J Digest Dis* 6 387, 1939

68 Wolff, L H The Effect of Certain Parenterally Administered Drugs on the Colon of the Dog, *Am J Digest Dis* 6 243, 1939

hemorrhagic condition of the upper parts of the gastrointestinal tract, namely, the stomach, duodenum and jejunum

The injection of hypophysin was shown by Myers to cause in cats an immediate but temporary abolition or diminution of peristaltic movements and a loss of tone due to administration of morphine and its alkaloids. Wolff, in his experiments on dogs, noted a definite decrease in tone and motility following the use of solution of posterior pituitary, a confirmation of previous findings. This, however, is entirely unlike the effect noted in human beings, in whom invariably an increase in the motility of the colon is to be observed following injection of solution of posterior pituitary. Pitressin administered subcutaneously was noted by Bisgard and Johnson to cause a great increase in both frequency and amplitude of gastric peristalsis but no change in tone. After a preliminary lessening of tone and activity, both were markedly increased in the ileum, and the amplitude of the rhythmic contractions was diminished. The effect was rather short in duration. In the dog the drug exerted no influence on gastric motility and caused only an increase in tone in the small bowel. In the large bowel both tone and peristalsis were definitely increased, but, as in man, the duration of the effect was relatively short. Administered intramuscularly, pitressin was noted by Reagan and Puestow to cause an increased tonus in the colon of the dog, without any particular effect on motility. Elsom, Glenn and Drossner⁶⁹ investigated the action of the drug on the small intestine and the colon in human beings by means of intubation and fluoroscopy and noted an increase in motor activity. Usually both tone and peristaltic activity were augmented, in some instances, however, the peristaltic increase was associated with a decrease in intestinal tone. After a brief contraction of the duodenum prolonged after-relaxation was observed. In general, the effects of pitressin were most intense in the most distal portion of the tract, the activity in the ileum and colon at times bearing a roughly reciprocal relation. Necheles and Masur⁷⁰ noted that constant intravenous injection of moderate amounts of pitressin in dogs was followed by a hemorrhagic condition of the entire gastrointestinal tract, especially of the lower part of the ileum and the colon. Such a finding would be entirely in keeping with any prolonged increase in muscular tone and contraction and, incidentally, is of interest in view of the hypothesis advanced by Lium as to the mechanism underlying mucosal hemorrhage

69 Elsom, K. A., Glenn, P. M., and Drossner, J. L. Intubation Studies of the Human Small Intestine. The Effect of Pitressin and of Amphetamine (Benzedrine) Sulphate on the Motor Activity of the Small Intestine and Colon, *Am J Digest Dis* 6: 593, 1939.

70 Necheles, H., and Masur, W. Gastro-Intestinal Pathology in Dogs Following Administration of Acetylcholine and Pitressin, *Am J Digest Dis* 6: 389, 1939.

and ulceration in colonic diseases Wolff, in his experiments, noted a decrease in the tone and motility of the colon when the drug was injected intravenously, but his findings seem to be at variance with those of most investigators Wolff also noted similar results from intravenous injection in dogs of preparations of pitocin but produced striking increases in tone and motility by use of physostigmine

Prostigmine when administered intramuscularly to dogs was found by Reagan and Puestow always to produce uniform maximum contractions, varying from a marked increase in tonus to a state of tonic contraction Of all the drugs used, prostigmine gave the most uniformly strong contractions Wolff noted that intravenous injection of epinephrine caused a decrease in tone and motility of the colon in dogs, and Myers, experimenting on cats, also observed that administration of the drug caused a temporary inhibition both in the small bowel and in the ileocecal region following morphine stimulation A similar decrease in the tone and motility of the dog's colon was noted by Wolff after intravenous administration of ephedrine By fluoroscopic determination of the gastric emptying time for healthy adults, Van Liere and Sleeth⁷¹ found that fluidextract of ergot caused an average delay of 30 per cent in the emptying time of the stomach and that ergotamine tartrate had a similar but less marked action It was felt that the delay in gastric emptying was due to a direct influence on the gastric musculature by the drug rather than to any action on the autonomic nervous system

The effect of anesthetics on gastrointestinal motility has been studied in some detail In man, Bisgard noted a marked reduction in tone, with a complete reduction of gastric peristalsis In the ileum rhythmic contractions continued, but with a diminution in both frequency and amplitude At the end of twenty-four hours the contractions of the stomach were still smaller than normal Within one hour after return of consciousness, however, there had developed an abnormally increased degree of muscular activity in the ileum In the dog, during the induction of anesthesia there was a definite and marked increase in the muscular tone and the amplitude of contractions in both the stomach and the bowel With the onset and during surgical anesthesia, a marked reduction of tone and cessation of motor activity were noted, except in the ileum, where again both rhythmic and tonic contractions continued, although they were relatively feeble Both tonic and motor activity were slowly reestablished with return of consciousness The colon and ileum promptly showed an abnormally increased tone, which was still evident twenty-four hours after return of consciousness, and twelve hours elapsed

71 Van Liere, E J, and Sleeth, C K The Effect of Fluid Extract of Ergot and of Ergotamine on the Emptying Time of the Human Stomach, *J Pharmacol & Exper Therap* 67 250, 1939

before the stomach had reestablished normal activity. The effects of ether preceded by a preliminary medication with morphine and atropine were noted in 2 patients during exploration of a retroperitoneal tumor in 1 and appendectomy in another. After the observation of a regularly increased tone and muscular activity during the stage of excitement, the tone gradually lessened but throughout remained elevated above the pre-anesthetic level. Motor activity was much diminished, but, although the ileum continued to contract with normal frequency, there was a great reduction in amplitude, which persisted throughout the period of observation (three hours). In the dog, the effect of ether anesthesia, as observed in the previous experiments, was definitely altered by pre-medication. The colon relaxed and ceased to contract as it did under the influence of ether alone, but in both the stomach and the small bowel premedication definitely delayed the return of normal activity.

In man, nitrogen monoxide and oxygen were noted to cause greatly but irregularly increased contractions of the stomach as regards frequency and amplitude, and the tone was moderately increased. The gastric tone remained slightly elevated after the anesthesia was discontinued. Motor function was reestablished slowly but was still subnormal three hours later. In the dog, during anesthesia the reactions were the same as those noted in man. After anesthesia was discontinued, the stomach continued to contract rapidly and violently, and this was concomitant withretching. Activity in the ileum and in the colon was almost completely abolished, and tone was diminished for thirty minutes. Normal function was reestablished in the stomach and ileum in one hour and in the colon in approximately two hours, but a record made eight hours after anesthesia showed increased activity in all three organs. The administration by inhalation of nitrogen monoxide, oxygen and ether to dogs showed results quite similar to those following the use of nitrogen monoxide and oxygen alone. The effects of cyclopropane were observed in man, and inhalation anesthesia by this method caused an increase in tone and rhythmic contractions but an inhibition of peristalsis during surgical anesthesia. Immediately on return of consciousness there was a diminution of tone to a subnormal level and a return of normal motor activity, which continued during observation periods for as long as three hours. In the dog, administration of cyclopropane induced an increase in tone and activity in the stomach and ileum, but decreased tone and activity were noted in the colon during surgical anesthesia. After cessation of anesthesia the colon reestablished and retained, during an observation period of six hours, normal tone and activity, the stomach and the ileum did likewise. Observations were made on the effects of cyclopropane when used as a supplement to a basal anesthesia induced by avertin with amylene hydrate. In man some diminution of motor activity was observed in the colon following use of avertin with

amylene hydrate With the addition of cyclopropane, gastric tone and activity were temporarily increased, but without establishment of complete surgical anesthesia the tone and activity became relatively normal. Incidentally, there was noted to be a moderate degree of hyperacidity forty-eight hours after recovery from the anesthesia In the dog no appreciable effect was produced by avertin with amylene hydrate, alone or supplemented by cyclopropane

The use of spinal procaine hydrochloride anesthesia without premedication was studied during the course of several appendectomies in human beings With the procaine hydrochloride, ephedrine was administered subcutaneously During anesthesia the stomach showed a slight reduction of tone and a greatly diminished muscular activity With the return of sensation there developed normal tone and motor hyperactivity. The contractions were exaggerated both in frequency and in amplitude, and this state continued for at least seventy-two hours after operation. The ileum, on the contrary, showed increased tone, with a slight reduction of all motor activity during anesthesia The tone receded with the return of sensation and remained relatively normal The rhythmic contractions showed increased amplitudes, and peristalsis was diminished as to both frequency and amplitude In the dog, spinal anesthesia following administration of procaine hydrochloride resulted in a slight diminution in gastric motor activity and muscle tone There was an increase in both the tone and the motor activity of the small bowel in 1 dog, other animals showed little or no change in the colon

In dogs administration of oxygen and carbon dioxide resulted in an increase in the tone and frequency of contractions of the stomach, ileum and colon but a decrease in the amplitude Normality was established when administration of oxygen was discontinued Administration of carbon dioxide alone resulted in a reduction of tone and an irregularly increased motor activity of the entire gastrointestinal tract The authors suggest that the influence of an individual anesthetic on the gastrointestinal tract may be dependent on its effect on the relative quantity of oxygen in the blood or tissues during anesthesia When inhaled, oxygen stimulates and carbon dioxide inhibits gastric motor activity

Reagan and Puestow noted that intravenous infusion had little, if any, effect on the motility of the dog's colon, but, like other observers, they found (as did Wolff) that concentrated solutions of sodium chloride (10 to 20 per cent) produced a marked increase in tonus and in the number and strength of contractions They were able to produce an increase in colonic motility following intravenous use of 5 per cent dextrose solutions, although the effect was of short duration Contrary to the usual finding of intestinal relaxation following use of intravenous calcium salts, Wolff noted that in the dog's colon there was an increase in both tone and motility

CLINICAL ASPECTS

Esophagus—The clinical aspect of esophageal disease is amply covered in an extremely informative review by Bird⁷² This author calls attention to recent advances in esophageal disease, particularly from the surgical point of view, in about eighty pages of carefully prepared matter In spite of the fact that Bird's article is written primarily for surgeons, it represents a complete survey of the subject and should be read by any who are interested in esophageal disorders The article not only reviews the current literature but makes it especially complete by reference to the observations of well known authorities throughout recent years This is of particular value, as many of the conditions mentioned are rarely seen except by a few physicians whose work is almost entirely limited to this particular field Congenital defects, such as tracheoesophageal fistulas with atresia, idiopathic obstruction, congenitally short or long esophagi, benign and malignant tumors, foreign bodies and their complications, traumatic lesions, strictures due to corrosive agents, esophagitis, peptic ulcer and specific infections are all treated in complete detail The review is particularly timely because of important recent advances in surgical technic whereby a transthoracic approach is making possible results hitherto unattainable A full description of the newer instruments and a detailed discussion of the technic and indications for esophagoscopy and bougienage are included

Of particular importance at present is the full discussion of the various carcinomatous lesions of the esophagus, with a complete description of the symptoms, diagnostic methods and therapeutic approach Bird indicates the extent to which Fischer's prophecy in 1923 has been fulfilled, namely, that "not many years from now many cures will have been accomplished in a disease that was beyond help and hope" Statistical studies based on all available figures from the United States and the Continent indicate that cancer of the esophagus as a cause of death is numerically very important The value of adequate radical surgical treatment of this condition is emphasized by reference to the observations of Watson, who noted that autopsy studies show that carcinoma of the esophagus often remains to the end a localized disease Scattered reports on radiation therapy are still extremely disappointing, and, although to date surgical cures are rare, there seems every reason for a more optimistic attitude toward this disease in the near future A separate report by Engelstad⁷³ on the radiologic treatment of carcinoma of the

⁷² Bird, C E Recent Advances in Surgery of the Esophagus Congenital Defects, *Surgery* 6 617, 1939, Carcinoma, *ibid* 6 772, 1939, Hemorrhage from Esophageal Varices, *ibid* 6 949, 1939

⁷³ Engelstad, R B Radiological Treatment of Carcinoma of the Esophagus, *Acta radiol* 20 469, 1939

esophagus stresses the present inadequacy of such therapeutic measures. This author reports the results of treating 119 esophageal carcinomas in the Norwegian Radium Hospital during the years 1932 to 1938. A permanent cure was not obtained in any case, and the average duration of life after treatment was only five months. Bird's review contains an excellent summary of the results obtainable by esophagoscopy, including the experiences of Jackson and others, and he does not fail to comment fully on the important diagnostic contributions by various roentgenologists, such as Macmillan, Moore, Schatzki and others.

A discussion of achalasia of the cardia is especially interesting, as this is a condition which rarely requires surgical intervention. Much of the history of the present knowledge of this condition is given in detail, including results of animal experimentation, the important clinical and histologic observations of Hurst and others on the degeneration of Auerbach's plexus and a consideration of medical and operative procedures. It is of interest that in such a surgical review the importance of medical treatment is so carefully stressed, and the article includes a discussion of the use of some specific medications. Bird points out the important fact that atropine and belladonna do not appear to be beneficial in the treatment of achalasia, although they do seem to be of benefit in cases of spasm of the esophagus at higher levels. The use of the nitrites is passed over, an unfortunate omission, as these preparations at times are of extreme value in controlling the symptoms of this curious condition. The value of instrumentation with dilation is thoroughly covered, and a resort to surgical measures is advocated only for chronic conditions which fail to respond to nonsurgical methods. An additional surgical approach to the therapy of this condition was stressed in a recent article by Chaikin,⁷⁴ who advocated bilateral cervicothoracic sympathetic ganglionectomy. Such a procedure, of course, is a logical one in view of the experimental work of Knight and others on the production of cardiac achalasia. The results following such treatment should still be subject to close scrutiny, and the procedure should at present be considered highly experimental. To return to a consideration of Bird's article, one cannot commend too highly this full and carefully written review of an important subject.

A much shorter but also carefully prepared commentary on the more common esophageal disorders, with illustrative cases, is that of Darrow,⁷⁵ and some additional articles warrant brief notice. The Plummer-Vinson syndrome is dealt with in several articles, which contain nothing new but

⁷⁴ Chaikin, N. W. Modern Concepts of Cardiospasm, *Rev Gastroenterol* **6** 332, 1939.

⁷⁵ Darrow, C. H. Lesions of the Esophagus, *Rocky Mountain M J* **36** 306, 1939.

CLINICAL ASPECTS

Esophagus—The clinical aspect of esophageal disease is amply covered in an extremely informative review by Bird⁷² This author calls attention to recent advances in esophageal disease, particularly from the surgical point of view, in about eighty pages of carefully prepared matter In spite of the fact that Bird's article is written primarily for surgeons, it represents a complete survey of the subject and should be read by any who are interested in esophageal disorders The article not only reviews the current literature but makes it especially complete by reference to the observations of well known authorities throughout recent years This is of particular value, as many of the conditions mentioned are rarely seen except by a few physicians whose work is almost entirely limited to this particular field Congenital defects, such as tracheoesophageal fistulas with atresia, idiopathic obstruction, congenitally short or long esophagi, benign and malignant tumors, foreign bodies and their complications, traumatic lesions, strictures due to corrosive agents, esophagitis, peptic ulcer and specific infections are all treated in complete detail The review is particularly timely because of important recent advances in surgical technic whereby a transthoracic approach is making possible results hitherto unattainable A full description of the newer instruments and a detailed discussion of the technic and indications for esophagoscopy and bougienage are included

Of particular importance at present is the full discussion of the various carcinomatous lesions of the esophagus, with a complete description of the symptoms, diagnostic methods and therapeutic approach Bird indicates the extent to which Fischer's prophecy in 1923 has been fulfilled, namely, that "not many years from now many cures will have been accomplished in a disease that was beyond help and hope" Statistical studies based on all available figures from the United States and the Continent indicate that cancer of the esophagus as a cause of death is numerically very important The value of adequate radical surgical treatment of this condition is emphasized by reference to the observations of Watson, who noted that autopsy studies show that carcinoma of the esophagus often remains to the end a localized disease Scattered reports on radiation therapy are still extremely disappointing, and, although to date surgical cures are rare, there seems every reason for a more optimistic attitude toward this disease in the near future A separate report by Engelstad⁷³ on the radiologic treatment of carcinoma of the

72 Bird, C E Recent Advances in Surgery of the Esophagus Congenital Defects, Surgery 6 617, 1939, Carcinoma, *ibid* 6 772, 1939, Hemorrhage from Esophageal Varices, *ibid* 6 949, 1939

73 Engelstad, R B Radiological Treatment of Carcinoma of the Esophagus, Acta radiol 20 469, 1939

esophagus stresses the present inadequacy of such therapeutic measures. This author reports the results of treating 119 esophageal carcinomas in the Norwegian Radium Hospital during the years 1932 to 1938. A permanent cure was not obtained in any case, and the average duration of life after treatment was only five months. Bird's review contains an excellent summary of the results obtainable by esophagoscopy, including the experiences of Jackson and others, and he does not fail to comment fully on the important diagnostic contributions by various roentgenologists, such as Macmillan, Moore, Schatzki and others.

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74 Chaikin, N. W. Modern Concepts of Cardiospasm, *Rev. Gastroenterol.* **6** 332, 1939.

75 Darrow, C. H. Lesions of the Esophagus, *Rocky Mountain M. J.* **36** 306, 1939.

emphasize the important features of this curious condition. Good descriptive summaries are to be found in an article by Gerlings⁷⁶ and in an editorial in *The Journal of the American Medical Association*⁷⁷. The clinical features of the condition are described in full detail, with adequate reference to the nutritional deficiencies, especially that of lack of iron, as of fundamental importance. The two articles stress one important point that should be noted, namely, the relation between this disease and cancer. Special reference is made to the observations of Ahlborn, who stated that in Sweden, at least, the Plummer-Vinson syndrome in women is a highly important factor predisposing to cancer of the mouth, pharynx and upper portion of the esophagus. He noted that 90 per cent of the women seen in Radiumhemmet for postcanceroid cancer reported symptoms like those of the Plummer-Vinson syndrome. It is obvious from such observations that careful examination of the mouth and tongue is of diagnostic and therapeutic importance when considering the symptom of dysphasia, as well as in many other conditions.

One experimental study is of interest with reference to the cause of the Plummer-Vinson syndrome. Cordray⁷⁸ carried out careful histologic examinations of 12 laboratory mice in which severe anemia was produced by administering for five and a half months a diet including milk and all the essential vitamins but extremely low in iron. At the end of this time the animals were extremely weak and definitely underweight. They were then killed, and sections of the esophagus were carefully studied. Microscopic examinations revealed that the esophageal epithelium showed marked hyperkeratinization and proliferation of the cells comprising the epithelium. There was an increase of mitotic figures over the usual normal number, suggesting a definitely pre-cancerous type of lesion. No fibrous tissue replacement in the musculature was evident, which conclusively ruled out esophageal "webs," a condition long held by Mosher to be the cause of the disease under discussion.

Schmidt⁷⁹ discusses spasm of the lower half of the esophagus as seen in a small group of cases at the Mayo Clinic. He indicates the important fact that such a condition, even with characteristic roentgen findings, may be entirely a reflex disorder secondary to extraesophageal disease and comments on the important fact that emotional disturbances

76 Gerlings, P. G. Changes at Mouth of Esophagus in Plummer-Vinson Syndrome (Dysphagia with Anemia), *Nederl tijdschr v geneesk* **84** 1289, 1940.

77 The Plummer-Vinson Syndrome and Cancer, editorial, *J. A. M. A.* **113** 1814 (Nov. 11) 1939.

78 Cordray, D. P. The Plummer-Vinson Syndrome, *Ann. Otol., Rhin. & Laryng.* **49** 160, 1940.

79 Schmidt, H. W. Diffuse Spasm of Lower Half of the Esophagus, *Am. J. Digest. Dis.* **6** 693, 1939.

alone can precipitate spasm of the distal portion of the esophagus in certain persons. The advantageous use of amyl nitrite, morphine sulfate, stramonium and papaverine hydrochloride is discussed.

An article by Vinson⁸⁰ on the management of benign stricture of the esophagus summarizes this condition particularly well and makes two important comments on its accurate diagnosis. In order that stricture at the pylorus may not be overlooked, roentgen examination of the stomach should be made for all patients who have swallowed a large amount of corrosive substances. Vinson properly warns against roentgen studies, however, until after the lumen of the esophagus has been restored by the passage of sounds. A second warning, of equal importance, lies in his statement that gastroscopy is seldom necessary in the management of benign stricture of the esophagus and adds particularly to the risk of treatment.

Kelly⁸¹ has continued his previous observations on the mechanism of ascending fibrosis of the esophagus in infants. Observations on sections taken at different levels of the esophagus were made on autopsy material removed from 17 children dying under 1 year of age. Islets of gastric mucosa were found at all levels of the esophagus, from the level of the cricoid cartilage to and below the diaphragm, although in this particular group they were found most frequently at the upper end of the esophagus. In cases in which these islets of gastric tissue were not ulcerated, no fibrosis was to be noted. Following ulceration, however, an inflammatory reaction ensued around the ulcer, which at times involved all the coats of the esophagus. A chronic inflammatory reaction was at times localized and at times spread widely up and down the entire tube. This spreading inflammatory reaction preceded the fibrosis. The cellular inflammation bore a striking resemblance to some forms of this condition occurring in the adult, although in later life fibrosis under such circumstances is most unusual.

Because of the increasing use of the esophagoscope and the gastroscope, the report by Jemerin and Coleman⁸² is of importance. These authors report 2 instances of formation of periesophageal cervico-mediastinal abscesses following nonperforative instrumental trauma to the esophagus. The trauma was insignificant, such as may occur at any well conducted esophagoscopy examination. These cases indicate that such a complication should, therefore, be looked for after any esophagoscopy if pain, dysphagia or fever follows passage of the instru-

80 Vinson, P. P. Management of Benign Stricture of Esophagus, *J. A. M. A.* **113** 2128 (Dec. 9) 1939.

81 Kelly, A. B. Ascending Fibrosis of Esophagus and Its Relation to the Presence of Islets of Gastric Mucosa, *J. Laryng. & Otol.* **54** 621, 1939.

82 Jemerin, E. E., and Coleman, L. L. Cervicomediastinal Abscess Due to Non-Perforative Trauma to Esophagus, *J. Thoracic Surg.* **9** 11, 1939.

ment The authors believe that the sequence of events in their cases was probably as follows Some degree of trauma to the esophagus took place, possibly with mucosal stripping and devitalization of the underlying esophageal wall by pressure The devitalized tissue comprised a favorable nidus for anaerobic infection, with subsequent localized esophagitis, which spread through to the contiguous periesophageal tissue It was possible on suspecting the complication to demonstrate small loculations of air in the periesophageal tissue, a roentgen finding pathognomonic of esophageal perforation, and in those instances in which no perforation could be demonstrated, these collections of air were probably due to the formation of gas by anaerobic bacteria

A case of a most unusual condition, congenital tracheoesophageal fistula without atresia of the esophagus, is reported by Imperatori⁸³ The case is remarkable in that such a condition is unusual without resulting atresia and still more so because of the plastic closure and apparent cure of the condition after eight years of life, with numerous operative procedures and infections of the respiratory tract due to aspiration

The complex symptoms arising from diaphragmatic hernia are becoming more and more familiar to the members of the medical profession, and the diagnosis of the condition is becoming more precise with the use of more careful roentgen technic Harrington⁸⁴ reviews the results of surgical treatment in a large group of cases and stresses the multiplicity of symptoms arising from this condition, which simulates other organic diseases in the thorax or abdomen An excellent histologic account of hiatus hernia is also given by Guthrie and Jones,⁸⁵ who similarly stress the importance of recognizing the condition frequently in order to avoid needless operations for suspected abdominal lesions or the placing of serious restrictions on a patient whose symptoms are thought to be due to cardiac disease In many instances, diaphragmatic (hiatus) hernia is discovered accidentally in the course of routine but careful roentgen examination and is not the cause of any symptoms, thus resembling diverticulosis The possibility of such a lesion being the cause of symptoms simulating those of cholelithiasis or coronary heart disease, however, must be continuously borne in mind The report of Schiro and Benjamin⁸⁶ on severe microcytic anemia associated with diaphragmatic hernia contains one interesting

83 Imperatori, C J Congenital Tracheoesophageal Fistula Without Atresia of the Esophagus, *Arch Otolaryng* **30** 352 (Sept) 1939

84 Harrington, S W Diaphragmatic Hernia Results of Surgical Treatment in Two Hundred and Ten Cases, *California & West Med* **50** 399, 1939, **51** 27, 1939

85 Guthrie, D, and Jones, F H The Frequency and Diagnosis of Hiatus Hernia, *Ann Surg* **111** 971, 1940

86 Schiro, H S, and Benjamin, J E Severe Anemia Associated with Diaphragmatic Hernia, *Ohio State M J* **36** 164, 1940

fact, that the patient was 1 of 3 sisters all of whom had diaphragmatic hernias, and the authors comment on the fact that a review of the literature on this condition suggests that the associated anemia not infrequently encountered is caused by congestion of the gastric mucosa proximal to the site of constriction and stated that in their case this could not be confirmed by gastrosopic examination. As a matter of fact, careful esophagosopic or gastrosopic study of the larger hernial sacs will almost always reveal marked congestion of the gastric mucosa and frequently diffuse hemorrhagic points.

The report of Feldman⁸⁷ on the occurrence of peptic ulcer of the lower portion of the esophagus in association with hiatus hernia is of interest because of the fact that in each of 2 cases the ulcer was demonstrable by a careful roentgen technic. The occasional superficial mucosal erosions to be seen by careful esophagosopic study usually occur in the hernial sac rather than in the esophagus and are not demonstrable by roentgen examination.

Traumatic herniation of the diaphragm with displacement of the abdominal viscera into the thoracic cavity is a well recognized condition, but the diagnosis is not always immediately considered. Articles by Brandt,⁸⁸ Falk and Smith⁸⁹ and Bliss and Green⁹⁰ bring out certain important clinical features. Brandt, in discussing the chronic form of a traumatic diaphragmatic hernia, provides illustrations of two types: a herniation which constantly causes symptoms, and the type in which there is postponement of symptoms for a long time after the original trauma, until incarceration may suddenly cause severe symptoms. He stresses the fact that a person may remain free from symptoms between the time of the injury and the appearance and signs of incarceration. Falk and Smith discuss the acute form of traumatic diaphragmatic hernia and also point out two variations: first, that observed in patients who have acute intestinal obstruction due to an acute or subacute traumatic hernia and, second, that observed in severely ill patients who present multiple injuries and extreme surgical shock at the outset and in whose cases it is proper at times to consider the possible existence of acute herniation of the viscera through the diaphragm in addition to the other existing injuries. Successful treatment depends on confirmation of such a condition by adequate roentgen study and by

87 Feldman, M. Peptic Ulcer of the Lower Esophagus Associated with Esophageal Hiatus Hernia, *Am J M Sc* **198** 165, 1939.

88 Brandt, H. Clinical Aspects in Diagnosis of Chronic Traumatic Hernias of the Diaphragm, *Munchen med Wchnschr* **86** 1312, 1939.

89 Falk, R., and Smith, R. S. Acute Traumatic Diaphragmatic Hernia, *Northwest Med* **28** 378, 1939.

90 Bliss, R. W., and Green, M. M. Traumatic Rupture of the Diaphragm with Bilateral Pneumothorax, *Southwestern Med* **23** 366, 1939.

immediate treatment. Such a case is that reported by Bliss and Green, in which a patient sustained a traumatic rupture of the diaphragm with bilateral pneumothorax following a serious accident. Successful treatment followed careful roentgen examination, including studies made after a barium sulfate enema, which revealed the transverse colon well up into the left thoracic space, and after a barium sulfate meal, which showed the stomach to be located in the left thoracic cavity.

Moore⁹¹ outlines in detail the types of treatment made available by proper use of the esophagoscope. Briefly he outlines these as dilation of strictures, cleaning out of pulsion diverticula prior to operation, removal of foreign bodies, and dilation for cardiospasm. A possible further use which may be available to the trained esophagoscopist is indicated in a report by Moersch,⁹² who repeated the work of Franchner and Crofoord, of Stockholm, and successfully injected esophageal varices in a patient who had associated cirrhosis of the liver. This form of therapy has been considered by various clinicians, but Moersch is the first one in the United States to attempt such a maneuver successfully. Sufficient time has not elapsed since the report was published to permit determination of the efficacy of the injection treatment, but the author is to be congratulated on his patience and skill in projecting a form of therapy that may conceivably lead to a more successful attack on the problem of hematemesis from varicose veins in the esophagus.

Stomach—Gastroscopy properly continues to attract the increasing attention of all physicians. Little new has been added in the past year, but at present the almost universal use of the gastroscope in various parts of the world has led to greater familiarity with the potentialities of this means of investigation. Fortunately, it has at the same time brought forth the beginnings of a critical evaluation of its usefulness, gastroscopists up to the present time having for the most part contented themselves with describing variations in the appearance of the stomach, as to both color and form. The actual number of observations on what constitutes normal variation in the appearance of the gastric mucosa is still far from adequate. Undoubtedly marked alteration in contour and general appearance occur during the various decades of life and follow acute or chronic constitutional diseases. These variations, in all probability, have no clinical implications from the point of view of symptomatology. There is still justification for skepticism in the interpretation of the chronic entity gastritis. Undoubtedly, pathologic changes exist in the stomach that can be

91 Moore, P. M., Jr. Esophagoscopy. Treatment of Lesions of the Esophagus, *Cleveland Clin Quart* 7: 52, 1940.

92 Moersch, H. J. Treatment of Esophageal Varices by Injection, *Proc Staff Meet, Mayo Clin* 15: 177, 1940.

identified by the gastroscopist but are in no way productive of symptoms. As Alvarez points out,⁹³ such alterations are entirely comparable to so-called chronic cholecystitis, "chronic appendicitis" and, under certain circumstances, peptic ulcer. A lack of knowledge exists regarding the exact histologic condition of the mucosal and submucosal tissues of the stomach accompanying the changes noted by the gastroscopist. Until such information is available, it will still be wise to regard gastroscopy as an important contribution to the study and diagnosis of disease of the stomach by a procedure which still must be utilized clinically with a good deal of caution. A similar conservative attitude is expressed by Browne.⁹⁴

Rodgers⁹⁵ discusses the practical indications for gastroscopy and reviews the opinions generally accepted at present. Unfortunately, this author makes one statement which will not bear critical judgment, namely, that in cases of anemia the use of the gastroscope is of interest but of little practical value. As a matter of fact, the gastroscope may well throw a great deal of light on the type of process occurring with various types of anemia and may help to differentiate cases of primary deficiency disease, of which the associated gastric atrophy is an important indication. It is in these cases, which are by no means infrequent, that atrophy of the stomach should properly be designated by the term gastric atrophy rather than by the more commonly used but incorrect term atrophic gastritis, there being no evidence of a primary inflammatory reaction.

The actual danger incident to use of the gastroscope has been reviewed by Schindler,⁹⁶ who questioned sixty gastroscopists throughout the United States. On the basis of these questions he was able to establish the existence of only 1 fatality directly due to gastroscopy in the course of over 22,000 examinations. In addition to this fatality, there were 8 perforations of the stomach and 1 perforation of the jejunum in a resected stomach. All 9 patients recovered, either after conservative treatment or after surgical intervention. Schindler's inquiry also revealed the occasional danger inherent in the use of pontocaine hydrochloride as a preliminary preparation to the gastroscopic procedure. Apparently this drug is definitely dangerous when used in the presence of open mucosal wounds or on the mucosa of the trachea and the bronchi. Three deaths following use of the drug had been reported in cases of carcinoma, and Schindler himself reported

93 Value of Gastroscopy Today, editorial, *Am J Digest Dis* **7** 51, 1940

94 Browne, D. C. Gastroscopy, *New Orleans M & S J* **91** 533, 1939

95 Rodgers, H. W., Hartfall, S. H., and Lintott, G., in Discussion on Gastroscopy, *Proc Roy Soc Med* **32** 519, 1939

96 Schindler, R. Results of Questionnaire on Fatalities in Gastroscopy, *Am J Digest Dis* **7** 293, 1940

1 case of an emaciated patient with stricture of the esophagus who had a bad reaction to the drug. He suggested that the drug should not be used for depleted patients but expressed the belief that ordinarily a dosage of not more than 25 cc of a 2 per cent solution of the drug with epinephrine hydrochloride is safe. Any serious reaction should be treated at once by the intravenous administration of some such preparation as pentothal sodium.

One physiologic study of interest is that of Kirsner, Nutter and Palmer⁹⁷. These authors investigated the hydrogen ion concentration of the gastric secretion after histamine stimulation in 72 patients with initial anacidity due to pernicious anemia, so-called atrophic gastritis, cancer of the stomach, irradiation of the stomach or one of a group of miscellaneous conditions, and made studies on the gastrosopic appearance of the mucosa in the same group of patients. They found no correlation between the hydrogen ion concentration of the gastric secretion, the presence or absence of a secretory depressant factor in gastric secretion, the presence or absence of anemia and the gastrosopic appearance of the stomach.

Phlegmonous gastritis is discussed by Cutler and Harrison,⁹⁸ who present 3 interesting case reports. The first case is of interest chiefly because it represents the usually accepted clinical picture of severe acute diffuse phlegmonous involvement of the stomach by hemolytic streptococci. Adequate surgical measures together with use of sulfanilamide and vitamin C were followed by recovery, a rare result with what is an almost universally fatal disease. The use of vitamin C was suggested because of the evidence of a little collagen formation in the granulative tissue removed at operation. The 2 other patients had localized areas of suppurative gastritis. In 1 patient there was pyloric stenosis due to an obstructive duodenal ulcer, and a biopsy specimen removed from the stomach at some distance from the pylorus revealed an area of suppurative local gastritis. Gastroenterostomy was performed for relief of obstruction, and recovery was uneventful. The last case was also one of chronic pyloric obstruction caused by a localized phlegmon of the gastric wall, the diagnosis being confirmed by biopsy material removed at the time of a pyloroplasty. The patient recovered and was well eight years later. The authors point out that it is of some importance to be cognizant of the fact that these two forms of suppurative gastritis occur.

97 Kirsner, J. B., Nutter, P. B., and Palmer, W. L. Studies on Anacidity. The Hydrogen-Ion Concentration of the Gastric Secretion, the Gastrosopic Appearance of the Gastric Mucosa, and the Presence of a Gastric Secretory Depressant in Patients with Anacidity, *J. Clin. Investigation* **19** 619, 1940.

98 Cutler, E. C., and Harrison, J. H. Phlegmonous Gastritis, *Surg., Gynec. & Obst.* **70** 234, 1940.

Consideration of chronic gastritis in its various forms has received the continued attention of numerous investigators,⁹⁹ all following the suggestion of Hurst and earlier students of the subject in stressing the possible etiologic importance of atrophic gastritis in relation to gastric cancer. Such a contention, although still incapable of being proved, is of real clinical importance and alone warrants the extensive use of the gastroscope for a careful continued observation of cases.

Schindler and Baxmeier¹⁰⁰ studied the mucosal changes of the stomach accompanying gastric ulcer and observed that 43 of 91 patients examined had no demonstrable gastritis and that in 10 others, in whom gastritis was not present at the first examination, it subsequently appeared. That gastritis might be associated with a gastric ulcer is not surprising, but the absence of any demonstrable gastric irritation, except for the localized ulcer, leads one to the conclusion that gastritis per se has little, if any, part in the causation of peptic ulcer of the stomach. Changes of the purpuric type were noted in almost half of the patients studied, but the exact significance of these changes is still far from clear.

Animal experiments carried out by Schindler, Necheles and Gold¹⁰¹ on surgical gastritis are of interest as indicating the importance of surgically traumatized tissue during operation. Normal stomachs in which acid secretion had not been stimulated previous to the operation did not show gastric erosions or other significant pathologic changes after subtotal gastrectomy or some similar procedure, such as the use of clamps or the ligation of arteries. In the case of controls with the use of a stomach not operated on, stimulation of acid secretion of the stomach or artificial introduction of hydrochloric acid into the stomach did not per se produce any pathologic changes. On the contrary, those parts of the stomach which were deprived more or less completely of their blood supply for two hours and which were exposed to hydrochloric acid either by stimulation of gastric secretion or by introduction of hydrochloric acid into the stomach showed more or less intense ulceration, petechiae and hemorrhage. These changes were directly

99 Schindler, R. Chronic Gastritis, *Bull. New York Acad. Med.* **15** 322, 1939. Schindler, R., and Gold, R. L. Gastroscopy in Gastric Carcinoma Especially in Its Early Diagnosis, *Surg., Gynec. & Obst.* **69** 1, 1939. Jankelson, I. R., and McClure, C. W. Present Status of Chronic Gastritis, *Rev. Gastroenterol.* **6** 473, 1939.

100 Schindler, R., and Baxmeier, R. I. Mucosal Changes Accompanying Gastric Ulcer. A Gastroscopic Study, *Ann. Int. Med.* **13** 693, 1939.

101 Schindler, R., Necheles, H., and Gold, R. L. Surgical Gastritis. Study on Genesis of Gastritis Found in Resected Stomach, with Particular Reference to So-Called "Antral Gastritis" Associated with Ulcer, *Surg., Gynec. & Obst.* **69** 281, 1939.

proportional to the degree of anemia of the stomach and the degree of acidity prevailing in the resected part. That part of the stomach in which the blood supply was left intact and into which acid had been secreted after stimulation by drugs did not show any changes from the normal. These observations would seem to be extremely significant as offering at least a partial explanation of some of the post-operative changes following operations on the stomach.

Chronic idiopathic gastritis has also received considerable attention. That use of the term "atrophic gastritis" should possibly be open to a certain amount of criticism has already been suggested. The fact remains that many conditions exist that may properly be so classified. Schindler and Murphy¹⁰² discuss in detail the symptoms of gastric disease characterized by diffuse atrophy of the gastric mucosa. They conclude that the digestive symptoms of this disease are not sufficiently characteristic to be of much diagnostic value. Among other symptoms, they characterize as extremely important soreness of the tongue and tingling of the extremities, and such a statement in itself justifies the foregoing criticism by the reviewer, as these symptoms are most commonly observed with deficiency conditions associated with macrocytic or microcytic anemia. However, the very indefiniteness and multiplicity of symptoms associated with true atrophic gastritis justifies Schindler's insistence on careful gastroscopic studies, particularly in view of the possible association of this condition with cancer.

That a fairly typical history of peptic ulcer may be obtained from patients who have no demonstrable ulcer but exhibit the gastroscopic appearances of gastric atrophy has been well recognized and is further established by the rather extensive clinical studies carried out by Morrison, Swalm and Jackson¹⁰³. These authors also point out the not infrequent occurrence of hemorrhage and melena in these patients.

An excellent report of the results of liver and iron therapy in cases of atrophic gastritis not associated with pernicious anemia, combined cord degeneration, sprue or pellagra is that given by Schindler, Kirsner and Palmer¹⁰⁴. Frequent but not invariable improvement followed institution of such therapy, as far as the gastroscopic appearance of the stomach and mucosa was concerned. It is of particular importance that in several instances discontinuance of liver therapy resulted in reappearance

102 Schindler, R., and Murphy, H. M. Symptomatology of Chronic Atrophic Gastritis, *Am J Digest Dis* 7 7, 1940

103 Morrison, L. M., Swalm, W. A., and Jackson, C. L. A Frequent Non-ulcerous Cause of the Peptic Ulcer Syndrome, *Pennsylvania M J* 43 243, 1939

104 Schindler, R., Kirsner, J. B., and Palmer, W. L. Atrophic Gastritis. Gastroscopic Studies on Effects of Liver and Iron Therapy, *Arch Int Med* 65 78 (Jan) 1940

ance of gastric atrophy. Careful control observations in the absence of treatment were carried out, and in 1 case the subsequent sudden disappearance of gastric atrophy following a brief period of liver treatment certainly suggests a specific therapeutic result and adds fresh evidence to support the opinion that gastric atrophy in many cases is the result of true deficiency disease. A point of interest in this particular case is that free hydrochloric acid was found in the presence of extensive atrophy, although this is not surprising in view of the known fact that patients with proved pernicious anemia are rarely able to secrete moderate amounts of free hydrochloric acid. In addition to observations following the use of liver, the authors report 1 case of gastric atrophy associated with hypochromic anemia. There was marked improvement not only in the anemia but in a complete healing of the atrophic gastritis following iron therapy. These findings are in agreement with those reported by Chevallier and Moutier, Schiff and Goodman and others.

Further studies along similar lines are reported by Schiff and Goodman¹⁰⁵. These authors present 5 cases of chronic gastric atrophy not associated with pernicious anemia, gastric cancer, protein deficiency or obvious vitamin C deficiency. The patients were treated with preparations of desiccated hog stomach (ventriculin). All showed marked symptomatic improvement, together with the disappearance of atrophic changes in the stomach. Administration of ventriculin was discontinued in the cases of 3 patients, 2 of whom showed a return of gastric atrophy and 1 an associated return of symptoms. A fourth patient showed definite improvement after discontinuance of the ventriculin, the atrophy recurring during ventriculin therapy, which would leave serious doubts as to the absolute specificity of this form of replacement therapy.

Entirely in keeping with most previous observations is the report of Johansen,¹⁰⁶ who followed 19 patients with pernicious anemia during liver therapy. In spite of clinical improvement and the disappearance of symptoms, at no time during a prolonged period of observation was there any change whatever in the achylia. Similar findings by other observers do not alter the fact that there is little, if any, association between the gastrosopic appearance of the stomach and the secretion or lack of secretion of hydrochloric acid. Such a conclusion has already been alluded to.

Sharp disagreement with the original findings of Jones, Benedict and Hampton and subsequent observations by Schindler, Chevallier and

105 Schiff, L., and Goodman, S. Desiccated Hog's Stomach Extract (Ventriculin) in the Treatment of Atrophic Gastritis, *Am J Digest Dis* **7** 14, 1940.

106 Johansen, A. H. Gastric Achylia in Pernicious Anemia After Liver Treatment, *Ugesk f læger* **91** 480, 1939.

Moutier is found in articles by Corey,¹⁰⁷ who claims that reestablishment of a normal-appearing mucosa or even an approximate return to normal was not seen in cases of pernicious anemia treated with liver. The findings of previous investigators, however, would seem to be well established and as much to be expected as the obvious and striking improvement commonly noted in the lingual atrophy after adequate treatment has been established.

Gastroscopic demonstration of intragastric foreign bodies is an obvious use of this method of investigation. Browne and McHardy¹⁰⁸ report several cases of phytobezoar, in which persistent digestive symptoms with inconclusive roentgen findings were explained by gastroscopic examination. An added report on the value of cytologic studies of the gastric contents is presented by Mulrooney.¹⁰⁹ One is rather skeptical, however, of the value of such a procedure in estimating the degree of gastric inflammation or progress due to therapy, especially in comparison with more precise methods of observation, such as careful roentgenographic and gastroscopic study or even adequate clinical observation.

Pyloric obstruction in infants is largely concerned with the condition known as hypertrophic stenosis. The condition is not infrequent and is well recognized by pediatricians. Several articles have appeared in the literature which stress certain important points of view regarding this particular disease. Terrien¹¹⁰ points out the important fact that symptoms of pyloric stenosis can exist in the absence of true organic disease of the pyloric portion of the stomach, and this condition has been designated as pseudostenosis. The author alleges that as long as doubt exists and the general condition remains satisfactory, with maintenance of weight, it is advisable to be conservative and to restrict treatment to medical measures which aim particularly at preventing formation of an undigested residue in the stomach with accompanying gastric hypersecretion and spasm. He points out the apparently important diagnostic observation that the symptoms of pyloric stenosis in nurslings do not begin with birth, on the contrary, the attacks of vomiting appear after two, three or four weeks of normal development. The author claims that this lapse of time between birth and the appearance of symptoms, a so-called "free interval," is never missing in cases of stenosis. If there

107 Corey, J. B. Gastroscopic Observations in Chronic Gastritis, *Am J Digest Dis* **7** 160, 1940, Gastroscopic Observations in Pernicious Anemia, *Minnesota Med* **23** 311, 1940.

108 Browne, D. C., and McHardy, G. Gastroscopy and the Phytobezoar. Report of Case of Diospyrobezoar, *Arch Int Med* **65** 368 (Feb) 1940.

109 Mulrooney, R. E. Cytology of Gastric Contents in Reference to Gastritis, *Proc Staff Meet, Mayo Clin* **15** 81, 1940.

110 Terrien, F. Pyloric Stenosis and Pseudostenosis in Nurslings, *Presse med* **48** 86, 1940.

is doubt, he concludes, particularly when evidences of malnutrition are noted, immediate surgical intervention is indicated

The results of surgical intervention are discussed by Dijkhuizen,¹¹¹ who reports a mortality of 5.4 per cent in a series of 130 infants operated on by Romstedt's method of pylorotomy. Wyatt¹¹² records an even lower mortality (3 per cent) in a review of 100 similar cases. Attention is also paid to the medical treatment of this condition, which consists largely in replacement of fluid and chlorides and in adequate atropinization. Successful treatment has been noted on previous occasions, and Folsom¹¹³ emphasizes the importance of atropine, insisting on the use of a fresh dilute solution, which makes possible the administration of several drops of 1:10,000, rather than 1 drop of 1:1,000, solution. Although most of the literature on this subject refers to surgical therapy, it is important that medical measures should not be overlooked, as their use may lead to favorable results. The marked reduction in mortality following surgical treatment of this form of pyloric stenosis is striking, and, as Wyatt points out, it has dropped in the last forty years from almost 100 per cent to a very low figure. There is little doubt that, in addition to increased skill in surgical technic, adequate attention to the restoring of fluid and the chloride balance has been of the utmost importance in securing such excellent results.

The preoperative and postoperative fluid treatment for pyloric stenosis is accurately discussed in an outline by Clausen and Ringsted,¹¹⁴ and these authors quite properly include the use of supplemental transfusions of blood to prevent hypoproteinemia when large infusions of fluid are needed. A further observation on the postoperative care of infants who have undergone pylorotomy for hypertrophic pyloric stenosis is presented by Faber and Davis.¹¹⁵ These authors noted the modifications of gastric peristalsis occurring after the Ramstedt operation and observed that there was a profound and prolonged depression of gastric motor activity, which lasted for about twenty-four hours, although in some instances it persisted for three or more days. In the average case, evacuation of material ingested soon after operation does not begin for

111 Dijkhuizen, R. Surgical Treatment of Hypertrophic Pyloric Stenosis in Nurshings, *Nederl tijdschr v geneesk* **83** 5053, 1939

112 Wyatt, O. S. Hypertrophic Pyloric Stenosis. Review of One Hundred Cases, *Journal-Lancet* **59** 233, 1939

113 Folsom, T. G. Pyloric Stenosis in Infancy, *West Virginia M. J.* **35** 416, 1939

114 Clausen, J., and Ringsted, A. Preoperative and Postoperative Fluid Treatment in Pyloric Stenosis, *Acta chir Scandinav* **82** 365, 1939

115 Faber, H. K., and Davis, J. H. Gastric Peristalsis After Pylorotomy in Infants, with Special Reference to Postoperative Care of Pyloric Stenosis, *J. A. M. A.* **114** 847 (March 9) 1940

over eight hours and is not complete until twenty-four hours after operation. The authors believe that this peristaltic inactivity is closely related to postoperative vomiting, which is common and often persistent for several days after pylorotomy. For this reason they urge against the traditional administration of water and food during the first postoperative day.

The report of Knutsson and Rudburg¹¹⁶ is of some interest. These observers make the interesting comment that pylorotomy performed for pyloric stenosis in children affects only the clinical condition. The roentgen appearance of stenosis persists for several years after the operation, in the absence of symptoms, and disappears only very gradually, as in the cases in which only medical treatment is given. Such a finding constitutes an additional reason for seriously considering the value of strictly medical treatment whenever possible.

Netto¹¹⁷ reports 4 cases of a condition which he describes as achalasia of the pylorus in adults. Two of the patients had a megasophagus and 1 a megacolon, the symptoms being dyspepsia, postprandial fulness, burning, eructations, nausea, vomiting and epigastric hyperperistalsis. Roentgen examination did not reveal stenosis of the pylorus, but because of the persistence of symptoms surgical intervention was advised, and at operation only abnormal thickening of the prepyloric antrum was found. This was due to hyperplasia of the muscle wall, and the author believes that the condition is identical to pyloric stenosis in the newborn except for the absence of a tumor. This lack in adults is attributed to generalized and uniform tissue hypertrophy. Microscopic examination of resected portions removed when a Finney pyloroplasty was done showed a pronounced loss of cells in the Auerbach-Meissner plexus, with replacement by true fibrous tissue. No typical characteristics of nerve trunk or ganglioneuritic cell degeneration were seen. In the absence of adequate roentgen data it is somewhat difficult to determine the indications for surgical treatment, but it is presumed that intractable symptoms persisting after adequate medical treatment were considered sufficient cause for abdominal exploration.

The pyloric stenosis associated with cholecystitis is fairly completely discussed by Baumel and Serre¹¹⁸. This, of course, is not a new entity, but it is sufficiently infrequent to warrant mention. The exact diagnosis is not always clear even after careful roentgen examination. The authors consider the evolution of symptoms, however, as important, two forms being distinguished: spasmodic stenosis, which as a rule responds

116 Knutsson, F., and Rudburg, S. Roentgenologic Effect of Ramstedt's Operation in Pyloric Stenosis, *Nord med (Hygiea)* **4**: 3101, 1939.

117 Netto, A. C. Achalasia of Pylorus in Adults, *Presse med* **48**: 148, 1940.

118 Baumel, J., and Serre, H. Pyloric Stenosis of Cholecystic Origin, *Arch d mal de l'app digestif* **29**: 241, 1939.

to medical treatment, and stenosis in which the mechanical element of true obstruction predominates, which requires radical operation. A careful analysis of the patient's history, together with absence of signs of ulcer and cancer, constitute the chief diagnostic criteria. The authors are correct in saying that the prognosis is at times grave even with adequately planned surgical treatment.

A rather unusual type of pyloric stenosis is that due to a gallstone after perforation into the stomach. One such case is described by Segal and Morton¹¹⁹. Apparently because of large amounts of scar tissue in the pyloric and duodenal regions, the stone was unable to pass through the pylorus and eventually produced the picture of intermittent pyloric obstruction. Roentgen examination suggested that the lesion was located and fixed in the pyloric end of the stomach, but gastroscopic study revealed that there was a foreign body outside the antrum and free from the mucosa.

A rather complete study of many of the chemical changes encountered in the blood of patients with pyloric obstruction is presented by Noth and Wilbur¹²⁰. A positive correlation between the amount of vomiting and the decreased values for blood urea and increased carbon dioxide-combining power was found, but the authors were unable to establish a definite relation between the values for these three chemical factors and the type of lesion present, the age of the patient, the amount of retained gastric secretion, the concentration of free hydrochloric acid in the gastric contents or a combination of any of these factors. They conclude that the low level of plasma chloride, while undoubtedly due to the loss of the chloride ion from vomiting, may be associated with other, additional factors. For practical purposes, they point out, the characteristic changes in the blood of patients suffering from pyloric obstruction are readily amenable in most cases to injection of physiologic solution of sodium chloride and 5 or 10 per cent dextrose.

Volvulus of the stomach, a rare clinical condition, is discussed in two papers. Singleton¹²¹ describes 2 cases of persistent gastric volvulus and a third, in which the condition tended to recur, and discusses the clinical manifestations. He mentions the interesting fact that volvulus of as much as 180 degrees may be present without cardiac or pyloric obstruction or strangulation of the blood supply. Schatzki and Simone¹²² also report a case and give an excellent discussion of the mechanical

119 Segal, H. L., and Morton, J. J. Perforation of a Gallstone into the Stomach with Resulting Pyloric Obstruction. One Case Report with Gastroscopic and Surgical Findings, *Am J Digest Dis* **6** 720, 1939.

120 Noth, P. H., and Wilbur, D. L. Chemical Changes in the Blood of Patients with Pyloric Obstruction, *Ann Int Med* **13** 285, 1940.

121 Singleton, A. C. Chronic Gastritis Volvulus, *Radiology* **34** 53, 1940.

122 Schatzki, R., and Simone, F. A. Volvulus of the Stomach, *Am J Digest Dis* **7** 213, 1940.

abnormalities involved and an extremely clear sketch of the variations in gastric position encountered

Diverticulosis of the cardiac end of the stomach, like diverticulosis of other portions of the gastrointestinal tract, may or may not be productive of symptoms. This important clinical fact is illustrated by a short report of Bonham¹²³ in a discussion of gastric diverticula, with an account of 3 cases in 1 of which the patient was completely relieved by operation, the patients in the other 2 being essentially free from symptoms with the simplest form of postural drainage. A curious manifestation of gastric diverticulosis is shown in a case reported by Halleron,¹²⁴ in which recurrent attacks of epigastric pain and jaundice without the appearance of a mass in the right upper quadrant were explained by a true diverticulum of the lower end of the stomach, which had become adherent to the under surface of the gallbladder and was intermittently the seat of an inflammatory reaction.

A discussion of gastric tumors other than cancer is of importance only for the purpose of emphasizing the fact that, although rare, they represent an appreciable number of benign or relatively benign invasions of the gastric wall. The symptoms are those of rather indefinite epigastric discomfort, but bleeding may be a feature. Suspicion and recognition of the possible existence of such tumors are of importance, because adequate surgical measures are frequently highly successful. Myhre¹²⁵ reviews the subject of benign gastric tumors, both epithelial and nonepithelial, and shows the extreme value of gastroscopic examination in the detection of these lesions, which are frequently difficult to demonstrate by roentgen examination.

A review of several articles¹²⁶ concerned with the various forms of sarcoma of the stomach reveals the diagnostic difficulties inherent

123 Bonham, D. T. Diverticula of the Cardia End of the Stomach, *Am J Digest. Dis* **7** 284, 1940.

124 Halleron, W. Diverticula of the Stomach. Case Report, *Minnesota Med* **22** 408, 1939.

125 Myhre, H. Benign Gastric Tumors, *Nord med (Norsk mag f lægevidensk)* **5** 282, 1940.

126 Taylor, E. S. Primary Lymphosarcoma of Stomach, *Ann Surg* **110** 200, 1939. Archer, V. W., and Cooper, G., Jr. Lymphosarcoma of Stomach. Diagnosis and Treatment, *Am J Roentgenol* **42** 332, 1939. Madding, G. F., and Walters, W. Lymphosarcoma of the Stomach, *Arch Surg* **40** 120 (Jan) 1940. Arent, C. H. Primary Isolated Lymphogranulomatosis (Hodgkin's Disease) of the Stomach, *ibid* **39** 423 (Sept.) 1939. Horsley, G. W., and Berger, R. A. Leiomyosarcoma of the Stomach, *Ann Surg* **112** 22, 1940. Hubeny, M. J., and Delano, P. J. Retothel Sarcoma of the Stomach, *Radiology* **34** 366, 1940. Chont, L. K. Primary Sarcoma of the Stomach, *ibid* **34** 714, 1940. Hochmann, A. Sarcoma of the Stomach, *Lancet* **1** 362, 1940. Phillips, R. B., and Rivers, A. B. Angiofibrosarcoma of the Stomach of Seventeen Years' Duration, *Rev Gastroenterol* **6** 468, 1939.

in these conditions. Treatment in individual instances must of necessity be surgical until the type of individual sarcoma and its identity have been established by microscopic examination. As the forms of lymphosarcoma constitute about two thirds of all sarcomas of the stomach, it is important that such studies be made in order to carry out adequate radiation treatment in addition to the necessary local surgical intervention. The prognosis of the combined group of lymphosarcomas is definitely better than that of carcinoma, leiomyosarcoma and fibrosarcoma. At least 1 case has been reported in which the patient lived for eight years after recognition of the gastric tumor. A report of a single case of angiofibrosarcoma of the stomach indicates the possible duration of symptoms with some of these rare conditions. In this particular instance the tumor was known to have been present in the epigastrium for seventeen years before surgical exploration took place. It is proper again to emphasize the important diagnostic help that may be obtained by skilful gastroscopic study in these cases, in which other diagnostic measures at present can offer little exact help.

The all-important subject of gastric carcinoma is, as usual, the basis of many communications. Animal experimentation on the possible etiology of malignant lesions of the stomach continues to be of interest. Although reports on the production of tumors of the stomach in experimental animals are very uncommon, Stewart¹²⁷ was able to produce squamous papilloma and squamous cell carcinoma of the stomach in a small percentage of mice in which an irritant in the form of methylcholanthrene in liquid petrolatum was injected into the anterior wall of the stomach. The time needed for the development of such tumors averaged about fourteen months, a fact which indicates that the mucous membrane of the stomach of the mouse is relatively resistant to the carcinogenic action of such an irritant as compared with other body tissues similarly treated. The adenomatous gastric lesion, which occurs spontaneously in mice of strain I, according to Andervont,¹²⁸ did not occur in mice of other strains kept in pens with strain I mice or fed specimens of the lesions. Dietary experiments on type I mice with such adenomatous changes in the stomach were carried out, with particular reference to avitaminosis A. The results obtained indicate that the lesion is not related in any way to the results of vitamin A deficiency. On the other hand, results obtained by Fridericia and his

127 Stewart, H. L. Induction of Gastric Tumors in Strain "A" Mice by Methylcholanthrene, *Arch. Path.* **29** 153 (Feb.) 1940.

128 Andervont, H. B. Studies on Some Possible Causative Factors of the Spontaneous Adenomatous Lesion of the Stomach in Mice of Strain I, *Pub. Health Rep.* **54** 2085, 1939.

collaborators¹²⁹ present fairly clear evidence that in rats subjected to a diet deficient in vitamin A, either intermittently or continuously, proliferative changes in the mucosal lining of the stomach were found in a much higher percentage (80 per cent) than in the control animals (18 per cent). The authors conclude that vitamin A deficiency must be in great measure a determining factor in the production of the gastric changes, although they admit that other factors, as yet unknown, also play an important part.

The possible influence of local gastric irritation on the formation of gastric tumors receives confirmation from the observations of Bonne and Sandground.¹³⁰ These authors report an epithelial tumor arising in the stomach of the common Javanese monkey, caused by a worm which lives in the depths of the tumor and has never been found free on the surface of the gastric mucosa. There is a constant association of the tumor and the worm. The tumor is a sharply localized, adenopapillomatous growth invading the submucosa, endothelial proliferation having been noted, with incipient invasion of the vessel wall. In 2 animals, found at a preliminary examination to be free of both tumor and worm, a tumor developed two and three months, respectively, after worms had been introduced into the stomach.

The generally accepted impression of the close relation between pernicious anemia and gastric cancer is substantiated by further observations reported by Jenner,¹³¹ who studied the fate of 180 patients with pernicious anemia. The incidence of gastric cancer in this group was 4 per cent, and what appeared to be adequate and careful statistical and biometric studies in relation to other patients of the same age groups indicated that the incidence of cancer is well beyond the limits of accidental occurrence. Such a conclusion, although in no way new, is important because of the fact that the life expectancy of patients with pernicious anemia under present methods of therapy has been so much prolonged that the occurrence of other serious diseases must be constantly watched for.

The fact that the annual death rate from gastric cancer in the United States is somewhere between 30,000 and 40,000 gives sufficient indica-

129 Fridericia, L. S., Gudjonsson, S., Vimtrup, B., Clemmesen, S., and Clemmesen, J. Stomach Lesions in Rats Kept on Diets Deficient in Vitamin "A", *Am J Cancer* **39** 61, 1940.

130 Bonne, C., and Sandground, J. H. On the Production of Gastric Tumors Bordering on Malignancy in Javanese Monkeys Through the Agency of *Nochtia Nocti*, a Parasitic Nematode, *Am J Cancer* **37** 173, 1939.

131 Jenner, A. W. F. Pernicious Anemia and Gastric Carcinoma, *Acta med Scandinav* **102** 591, 1939.

tion of the need for continuous study on the subject Rivers,¹³² in a statistical study of 4,600 cases, emphasizes the fact that men seem to progress into a definite dyspepsia-cancer age from five to ten years earlier in life than women. In man this period seems to start in the late fifties. Because of this fact, he properly urges an exhaustive search for cancer in patients in whose cases "dyspepsia" is the major complaint, even when another, less formidable cause has been discovered.

With the improved technic of gastric surgery as it exists today, Bryan¹³³ states that between 20 and 50 per cent of early carcinomas of the stomach can probably be cured by operation and that roentgen diagnosis of early carcinomatous lesions is accurate in between 90 and 95 per cent of cases. Even if Bryan's figures are somewhat optimistic, there is no doubt that modern gastric surgery offers much greater hope for success than formerly, once the diagnosis has been established. There is equally little doubt that improvement in roentgen diagnostic technic has kept pace with progress in the surgical field. The figures for operability and successful resection of gastric cancer naturally vary according to the community in which the figures are obtained, depending not only on the diagnostic and operative skill of the local surgeons but on the education of the public and the various economic groups represented by patients admitted to hospitals in given districts. The percentage of five-year operative cures reported varies from 3 per cent to approximately 20 per cent of all cases in which resection of the tumor has been done. It is to be noted, however, that resection has undoubtedly been increased in the surgical program in the last few years. However, much remains to be accomplished from the point of view of early diagnosis. Even with the best statistical results five-year cures of cancer of the stomach are equivalent to between 5 and 6 per cent of all cases in which operation is performed. Articles of interest in this connection are those by Rippy,¹³⁴ Walton¹³⁵ and Parsons and Welch.¹³⁶ A slight note of optimism is to be found in the article by the last-mentioned authors, who feel that the total number of diagnosed gastric cancers has increased greatly in recent years, that more patients have been operated on and that the percentage of resectable growths has increased, with a reduction in operative mortality.

132 Rivers, A. B. The Importance of Cancer as a Cause of Chronic Dyspepsia, *J. A. M. A.* **113** 1188 (Sept. 23) 1939.

133 Bryan, W. E. Carcinoma of the Stomach. An Analytical Study, *J. Tennessee M. A.* **32** 390, 1939.

134 Rippy, E. L. Cancer of the Stomach. Conclusions from Study of Two Hundred Cases, *South Surgeon* **8** 359, 1939.

135 Walton, J. Carcinoma of the Stomach, *Brit. M. J.* **2** 1127, 1939.

136 Parsons, L., and Welch, C. E. Curability of Carcinoma of the Stomach, *Surgery* **6** 327, 1939.

Attention has previously been called to the use of hydrochloric acid in preoperative preparation of patients with cancer of the stomach. Abramovich¹³⁷ reports the results of bacteriologic studies undertaken to determine the effect of this procedure, originally suggested by Friedrick in 1933. Studies on 64 patients with gastric achylia about to be operated on for gastric cancer showed that the anacid gastric contents were never sterile. Oral administration of a solution of 0.25 per cent hydrochloric acid over the course of several preoperative days destroyed certain types of micro-organisms and diminished the number of colonies of other types. Drinking of the solution, combined with lavage, accelerated the cleansing process, the maximum bactericidal effect being accomplished in from thirty to sixty minutes. Because of the fact that 70 odd per cent of the fatalities following operation for gastric cancer in the Leningrad Institute were due to peritonitis, the author suggests the value of such a procedure, especially if practiced immediately before the operation, as an important factor in reducing possible postoperative peritonitis.

Restoration of normal gastric tone and motility after subtotal resection has been studied by Vitkin¹³⁸. This author made observations on a stomach resected by the Billroth II method or some modification of it. Satisfactory rhythmic evacuation occurred after a subtotal gastrectomy, and apparently normal gastric tone was restored after operation, regardless of whether the condition of the stomach preceding operation represented atony or hypertonicity. The type of evacuation obtained apparently does not depend on the extent of the resected region, as rhythmicity of evacuation was observed even in cases of almost total gastrectomy. There were no data which would substantiate belief in the formation of a sphincter in the region of the anastomosis. Spasm of the anastomosis after gastrectomy undertaken for cancer the author believes to be an early symptom of local recurrence. One interesting note in this communication is the observation that hyperplastic gastritis and jejunitis follow subtotal gastrectomy, but without any subjective manifestations. Whether such a statement is true in its entirety or not, it provides one further reason for a critical analysis of the significance of gastroscopic findings.

In view of the work of Bisgard, already alluded to, on the effect of barbiturates on gastrointestinal tone and motility, one is inclined to question the correctness of Romino's¹³⁹ observations, as he advocates

137 Abramovich, S. A. Hydrochloric Acid in Preoperative Cleansing of Cancerous Stomach, *Novy khir. arkhiv* **42** 355, 1939.

138 Vitkin, S. F. Motor Function of the Stomach After Resection, *Ann Surg* **111** 27-1940.

139 Romino, J. D. Postoperative Vomiting and Phenobarbital, *West Virginia M. J.* **35** 461, 1939.

the use of phenobarbital in doses ranging from 3 to 5 grains (0.19 to 0.32 Gm) on the day before operation. Except after what amounted practically to anesthetic doses, Bisgard was unable to demonstrate any effect of seconal (sodium propylmethylcarbonylallylbarbiturate) and evipal (C-C-cyclohexenyl-N-methyl barbituric acid) on motility and tone, and even after anesthetic doses there was only a transient abolition of both during the period of unconsciousness. Romino's impression that postoperative nausea and vomiting were distinctly diminished is of interest but should be substantiated by careful observations on a large control series before this form of medication is accepted as a routine preoperative measure.

Numerous pathologic rarities involving the stomach are reported but are of little interest except as curiosities. In the case of Baumann-Schenker¹⁴⁰ there was an unusual manifestation which is worthy of passing comment. The case described was one of cystoid pneumatosis of the stomach and jejunum, in which there was no spontaneous pneumoperitoneum. The diagnosis was established preoperatively on the basis of the roentgen appearance of the vesicular structure of the stomach, duodenal bulb and upper portion of the small bowel. The condition apparently was attributable to chronic ileus of long standing, and the multiple small submucosal cysts were not demonstrable even at operation until a biopsy specimen had been taken. The report of syphilis of the stomach by McPeak¹⁴¹ is of interest chiefly because he not only presents the clinical, pathologic, gastroscopic and roentgen observations in a given case but is able to show progressive changes from early to extensive involvement of the stomach. Gastric tuberculosis is so rare that the report of Zelman¹⁴² on the combination of tuberculosis of the pancreas and a proved tuberculous gastric ulcer warrants passing comment. That unsuspected rupture of the stomach may follow trauma is known, but such a possibility is not usually thought of. The note by Casberg¹⁴³ is therefore of interest in recalling such a possibility. In his case the patient presented the typical picture of a ruptured spleen, but at operation an unsuspected rupture of the stomach was found as well. Shellac bezoars are medical curiosities much less common than trichobezoars and phytobezoars. Inlow¹⁴⁴ reports a case in which the

140 Baumann-Schenker, R. Pneumatosis cystoides ventriculi et jejuni, *Acta radiol* **20** 365, 1939.

141 McPeak, C. N. Syphilis of the Stomach, *Am J Roentgenol* **43** 832, 1940.

142 Zelman, J. Tuberculosis of the Pancreas and the Stomach, *Am Rev Tuberc* **41** 809, 1940.

143 Casberg, M. A. Traumatic Rupture of the Spleen and the Stomach *J A M A* **114** 1544 (April 20) 1940.

144 Inlow, H. H. Shellac Bezoars *Radiology* **38** 618, 1940.

foreign body was diagnosed by roentgen examination and removed by gastrotomy. Chemical analysis established the composition of the bezoar. Shellac bezoars have been found only in male drunkards who have access to alcoholic shellac solutions.

Peptic Ulcer —The literature on peptic ulcer continues without abatement. Any complete review of it is not justified, as a great deal of the material published is unimportant or contains no new point of view. Many of the articles consist in repetitions of previous clinical or experimental observations. As yet no specific etiology or therapy of this chronic intractable disease has come to light, although a certain amount of valuable information is constantly being added to the knowledge of the subject.

An article by Mann¹⁴⁵ is of value largely because it constitutes a review of the results of experimental investigation on the mechanism of peptic ulceration. He points out at least two mechanisms in the development of the experimentally produced ulcer. One involves initially a disturbance of the blood supply to the ulcerated region and is still not clearly understood. The second depends on mechanical and chemical factors, ulceration occurring only where the mucosa is exposed to acid gastric contents not protected by the normal mechanism for diluting, buffering and neutralizing the acidity. The actual site of the ulcer is determined by the mechanical factor of expulsion of gastric contents and occurs in the region where the gastric juice first strikes after emergence from the stomach. A third type of experimentally produced peptic ulcer comprises lesions produced by cinchophen. The entire life history of such ulcers has not yet been fully observed, but they appear to be a combination of the two types just described. The review is of particular importance because it summarizes the principles underlying the experimental approach to this difficult subject.

Fresh evidence of the possible relation of circulatory disturbances to the production of peptic ulcer in man is presented by Boles, Riggs and Griffiths,¹⁴⁶ who record careful histologic studies in 161 cases of acute focal lesions of the gastric mucosa. These authors concluded that, regardless of causation, focal gastric lesions are the result of chronic circulatory insufficiency to all the structures of the gastric wall. Such circulatory deficiency is part of a generalized insufficiency intensified by intrinsic vascular peculiarities, anatomic or vasomotor, of the stomach. The histologic preparations presented by these authors were excellently made and would seem to constitute important evidence in favor of at

145 Mann, F. C. Mechanism of Peptic Ulceration. Review of Results of Experimental Investigation, *Brit. M. J.* 1: 707, 1939.

146 Boles, R. S., Riggs, H. E., and Griffiths, J. O. Role of Circulation in the Production of Peptic Ulcer, *Am. J. Digest. Dis.* 6: 632, 1939.

least one of the possible causative factors of ulcer. A further contribution to such a conception is that of Berg,¹⁴⁷ who was able by frequent injections of pitressin in normal vagotomized dogs to produce marked hypermotility of the stomach and eventually ulcerations, some of which extended into the muscularis. Although chronic ulcerations were not produced, the lesions were more extensive and more frequently found in those animals in which vagotomy had been performed. Berg feels that the results were strongly suggestive of the possibility that functional vascular alterations play an important role in the causation of ulcer.

A slightly different mechanism in the production of ulcer, but one also involving the circulatory system, is that noted in the animal experiments of Penner and Bernheim.¹⁴⁸ Previous necropsy studies of patients dying with ulcer suggested that ulceration of the gastrointestinal tract might be due to alterations in the vasomotor mechanism present in this condition. In the necropsy material ulcerative lesions were noted in the esophagus, stomach and duodenum, appearing postoperatively or following diabetic acidosis, in the absence of any systemic disease, such as diffuse vascular disease, chronic glomerulonephritis, periaarteritis nodosa or any localized pathologic change in the stomach or duodenum. Examination of the necropsy material indicated that the earliest histologic changes consisted of marked distention of the capillaries and venules in the mucosa of the stomach and in the submucosa of the esophagus and the duodenum. Edema and focal hemorrhages were observed, due probably to increased permeability of the capillaries resulting from the stasis consequent to arteriolar constriction occurring in response to shock. Ultimate progression resulted in focal necropsy of the tissues involved. Because the authors felt that such vasomotor disturbances associated with shock constituted the basis for the ulcerations observed, they attempted to reproduce in animal experiments a pathologic picture similar to that noted in cases of shock. Repeated intraperitoneal injections of epinephrine were utilized, and the writers were able to observe the production of lesions in the digestive tract grossly identical to those observed in human material. These experimentally produced anatomic changes are offered as evidence in support of the clinical appearance of vasospasm which is of sufficient severity and duration to cause tissue necropsy. Such a mechanism may well be operative in cases of extensive burns known to be associated with acute peptic ulceration. One typical

147 Berg, M. Experimental Studies on the Production of Peptic Ulcer by Vasomotor Alterations (Pitressin Episodes), *Am J Digest Dis* **7** 78, 1940.

148 Penner, A., and Bernheim, A. I. Experimental Production of Digestive Tract Ulcerations, *J Exper Med* **70** 453, 1939, Acute Postoperative Esophageal Gastric and Duodenal Ulcerations. A Further Study in the Pathologic Changes in Shock, *Arch Path* **28** 129 (Aug) 1939.

case is reported by Keeley,¹⁴⁹ with a review of the literature on this subject

The neurogenic origin of peptic ulcer is well recognized, and several case reports are to be found in the literature for the year, all verifying Cushing's observations and the original assumption of Rokitsansky, who appears to have been the first to regard ulcerative processes of the gastrointestinal tract as of neurogenic origin. The exact mechanism operative in such cases still can only be surmised, however, and a detailed review of the case reports is not warranted in this article. Whether psychogenic factors (as has been indicated by certain writers) or neurogenic overstimulation from intracranial tumors effects the production of peptic ulcers by means of vasomotor disturbances is still open to wide speculation. An attempt by Ask-Upmark¹⁵⁰ to correlate the occurrence of peptic ulcer with existing hepatic disturbances incident to cirrhosis of the liver is of clinical interest but in no sense conclusive. In addition to noting 9 cases of gastric or duodenal ulceration among 22 patients who died from cirrhosis of the liver, the author performed a number of galactose tolerance tests on patients with peptic ulcer. He concludes that the frequency with which abnormality was noted, together with the behavior of the blood sugar curve, provides evidence of a causative relation between hepatic dysfunction and peptic ulceration.

A careful analysis of 75 cases of patients with proved peptic ulcer and of 72 other cases of persons known to be clinically allergic is of interest because of the conservative tone of the conclusions of the authors, Ehrenfeld, Brown and Sturtevant.¹⁵¹ These writers conclude that allergy is not a significant factor in the production of peptic ulcer. They make the additional valuable point, however, that gastrointestinal symptoms suggestive of ulcer are not infrequent among allergic persons and that roentgen studies of such persons frequently show transient spastic phenomena in the stomach or duodenum. Such findings lend support to the explanation of Demel that gastrointestinal allergic manifestations may be due to localized wheals or to angioneurotic edema.

Further studies on the effect of pregnancy and administration of chorionic gonadotropin (antuitrin S) on experimental ulcer are presented by Farbman, Sandweiss and Saltzstein.¹⁵² Neither pregnancy

149 Keeley, J. L. Gastro-Intestinal Ulcerations Following Burns, *Am J Surg* **45** 85, 1939

150 Ask-Upmark, E. Further Observations on the Pathogenesis of Peptic Ulcer, *Acta med Scandinav* **103** 280, 1940

151 Ehrenfeld, I., Brown, A., and Sturtevant, M. Studies in Gastrointestinal Allergy, Allergy in Pathogenesis of Peptic Ulcer, *J Allergy* **10** 342, 1939

152 Farbman, A. A., Sandweiss, D. J., and Saltzstein, H. C. The Effect of Pregnancy and of Antuitrin-S on Cinchophen Ulcers in Dogs, *Am J Digest Dis* **6** 702, 1939

nor injections of gonadotropin had anything but a very slight effect on cincophen ulcers in dogs, a decidedly different result from that previously noted when chorionic gonadotropin was injected into Mann-Williamson dogs. Such a finding justifies the cautious note regarding parenteral therapy of endocrine preparations continuously sounded by Sandweiss and his associates.

The predictable effect of predigested food on experimental peptic ulcer in Mann-Williamson dogs was tested by Emery, Zollinger and Rutherford¹⁵³ in an attempt to control any nutritional deficiency which might be present. No beneficial results were obtained, although the authors feel that further similar studies are indicated because of previous experimental work done by Fauley and Ivy.

Increasing recognition of the fact that ulcers occur at an early age is evidenced by the appearance of numerous case reports, the youngest patient being described in the case noted by Hunter and Dryer¹⁵⁴ of a duodenal ulcer in a 3 day old child. The vomiting of coffee-ground material and the appearance of melena were ultimately followed by death, and autopsy showed kissing ulcers in the duodenum. A review of the literature dating from Spiegelberg's original description (1869) of duodenal ulcer in the newborn and a discussion of possible causes are of interest.

The notation of peptic ulcers in rather unusual locations indicates the necessity for skilled roentgen observations to provide an exact demonstration of the site of peptic ulceration. Horsley¹⁵⁵ reports 2 ulcers proved to be exactly in the pyloric sphincter. Dimerleau¹⁵⁶ includes 4 instances and Brulé and his co-workers¹⁵⁷ a fifth instance of peptic ulceration of the second portion of the duodenum, while Berry and Dailey¹⁵⁸ add a case of primary ulcer of the jejunum. Routine roentgen study in such instances frequently misses lesions of this character, and it is only by persistent effort on the part of the roentgenologist and insistence by the clinician on the importance of ulcer-like symptoms that such unusually located ulcers are found. In the case of low duodenal and jejunal ulcers

153 Emery, E. S., Zollinger, R., and Rutherford, R. B. The Effect of Predigested Food on Experimental Peptic Ulcer, *Surgery* **7** 574, 1940.

154 Hunter, W., and Dryer, H. W. Duodenal Ulceration in New Born, *Brit. M. J.* **2** 15, 1939.

155 Horsley, G. W. Ulcers of the Pyloric Sphincter with Case Reports, *Virginia M. Monthly* **67** 29, 1940.

156 Dimerleau, J. Ulcers of Second Portion of Duodenum, *Arch. d. mal. de l'app. digestif* **29** 856, 1939.

157 Brulé, M., Hilleman, P., Gilbrin, E., and Callandry, L. Ulcers of Second Portion of Duodenum, *Arch. d. mal. de l'app. digestif* **29** 846, 1939.

158 Berry, L. H., and Dailey, U. G. Primary Ulcer of the Jejunum, *Am. J. Digest. Dis.* **7** 63, 1940.

it is important to restate the fact that the pain will continue to be periodic but will be localized, as a rule, in the periumbilical region

The relation between benign and malignant gastric ulcers is extremely well summarized by Palmer¹⁵⁹ Important points in differential diagnosis and the difficulties involved are thoroughly considered, including the results of all diagnostic procedures Although there is no pathognomonic sign to indicate the benign nature of the lesion, Palmer insists that the total evidence available from a careful study permits clinical differentiation of benign and malignant gastric lesions to be made with a high degree of accuracy Such a statement is undoubtedly correct but must be qualified by one of the opening sentences in his article, which bears repetition "One must bear in mind that the accuracy of the clinical differentiation varies from person to person, just as the mortality rate from resection varies from individual to individual Both depend upon the skill of the physician or surgeon" The article is well worthy of careful perusal

Although originally skeptical of the conclusions of Holmes and Hampton regarding the frequency with which prepyloric ulcerations show malignant characteristics, Sampson and Sosman,¹⁶⁰ in a recent report, confirm in every way the importance of the former authors' observations Their study is based on a series of 545 patients admitted to the Peter Bent Brigham Hospital, comprising all the patients with gastric ulcer and gastric cancer subjected to operation or autopsy during a twenty-five year period Gastric ulcers in the prepyloric 1 inch (2.5 cm) of the stomach were found to be cancerous in 75 per cent of cases

Observations on large groups of patients with ulcer over reasonably long periods have been recorded by various authors, but nothing new has been added to the routine measures that are successfully used in controlling the symptoms and progression of peptic ulcer It is obvious from the various reports that careful attention to a routine, which may be one of many, is capable of giving satisfactory results Some of the newer therapeutic measures are worthy of comment, although conclusions resulting from their use are frequently open to criticism The treatment of duodenal ulcer with intramuscular injections of histaminase by Nakada¹⁶¹ recalls previous favorable reports on the results attributed to the use of histidine preparations The favorable results reported are not subject to any control observations and should be considered with a great deal of frank skepticism It is unfortunate that such reports creep

159 Palmer, W. L. Benign and Malignant Gastric Ulcers Their Relation and Clinical Differentiation, *Ann Int Med* **13** 317, 1939

160 Sampson, D. A., and Sosman, M. C. Prepyloric Ulcer and Carcinoma, *Am J Roentgenol* **42** 797, 1939

161 Nakada, J. R. Treatment of Duodenal Ulcer with Histaminase, *Rev Gastroenterol* **6** 389, 1939

into the literature without adequate studies, as many patients suffering from such a chronic disease as duodenal ulcer are subjected to unnecessary or expensive forms of therapy without any ultimate realization of their original hopes for a cure. Trial of new methods should in no case be discouraged, but it is important to insist on adequate study of their use before favorable results are reported.

Metz and Lackey¹⁶² continue to report favorable results associated with the use of posterior pituitary preparations. Intranasal insufflation of posterior pituitary powder, they claim, completely relieved symptoms in from seven to twenty-one days in 67 patients with ulcer. Coincidentally with the disappearance of symptoms, the authors noted a gain in the general feeling of well-being, with a diminution of nervousness and insomnia. No dietary regimen and no other medication was employed, and the patients remained ambulatory during treatment. That hormonal secretions, including those of the pituitary, exert a definite influence on gastric and duodenal motor and secretory physiology is known, but the authors are wise in stating that posterior pituitary preparations should be considered complementary to the accepted principles of management of peptic ulcer.

Although treatment of peptic ulcer with histidine preparations has largely fallen into disrepute, the data obtained by Schmidt¹⁶³ provide further evidence against the hypothesis that there is a histidine deficiency in patients with ulcer which prevents normal healing. From his figures it seems obvious that there is no appreciable difference between the histidine content of patients with peptic ulcer and that of normal persons.

In an attempt to prove the essential role of gastric acidity in the genesis and course of chronic ulcer, Palmer and Nutter¹⁶⁴ present a complete review of the literature since 1926. They admit that small acute and subacute gastric ulcers may occur in the presence of achlorhydria proved by histamine but cited statistical studies of over 1,000 cases of chronic gastric and duodenal ulcer in which no instance of chronic benign ulcer was observed in the presence of complete achlorhydria. They further refer to the failure of other observers to find chronic or acute peptic ulcers in over 1,700 autopsies of patients dying from pernicious anemia. Although it is undoubtedly true that typical peptic ulcer is extremely uncommon in the presence of histamine achlorhydria, it is difficult to disregard the findings of other careful

162 Metz, M. H., and Lackey, R. W. Peptic Ulcer Treated by Posterior Pituitary Preparations, *Am J Digest Dis* **7** 27, 1940.

163 Schmidt, E. G. The Histidine Content ("Dialo Value") of the Blood in Peptic Ulcer, *J Lab & Clin Med* **25** 512, 1940.

164 Palmer, W. L., and Nutter, P. B. Peptic Ulcer and Achlorhydria. Further Study of Role of Acid Gastric Juice in Pathogenesis of Peptic Ulcer, *Arch Int Med* **65** 499 (March) 1940.

observers, who occasionally have noted after adequate studies the existence of undoubted typical peptic ulceration in patients refractory to histamine stimulation. The article, however, is to be carefully considered as indicative of the role of gastric acidity as one of the important factors in activation of peptic ulceration of the stomach and duodenum. The possible corollary, to be inferred by some, that so-called neutralization of gastric acidity is the only physiologic and therapeutic approach to the medical treatment of peptic ulcer is one that will hardly bear acceptance, and in this regard it is of some importance to read Bloomfield's¹⁶⁵ timely comment on the problem of hyperacidity. The point of view to be found in this article is worthy of repetition not only as regards ulcer therapy but as concerns the broader aspects of the so-called clinical syndrome of hyperacidity.

In view of the foregoing statements, it is of interest to note the appearance of more articles questioning the necessity and value of too enthusiastic attempts to neutralize gastric acidity in cases of peptic ulcer. Both Nicol¹⁶⁶ and Ronald¹⁶⁷ point out the fact that healing of peptic ulcer and relief of symptoms can take place even though hyperchlorhydria is unaltered and agree that the importance of free acid in the stomach in interfering with the healing of ulcers has been overemphasized. Further skepticism as to the actual role played in the control of symptoms of ulcer by antacid therapy is voiced by Steigmann and Fantus,¹⁶⁸ who studied the efficacy of four currently used substances in the treatment of peptic ulcer: Sippy powder no. 1 (1 part calcium carbonate and 3 parts sodium bicarbonate), aluminum hydroxide gel, neutralized karaya gum and an acid-bismuth mixture. After use of these preparations, the authors pointed out that the relief of pain, which was uniform, must have been secured by some other means than an antacid action, most probably by lessening of gastric tension. Even Kirsner and Palmer,¹⁶⁹ in a study of the effect of various antacids on the hydrogen ion concentration of the gastric contents, agree that the most efficacious combination for a reduction of p_H values to the "proteolytic neutralization level" of Hollander is obtained by the com-

165 Bloomfield, A. L. The Problem of Hyperacidity, *Am J Digest Dis* **6** 700, 1939

166 Nicol, B. M. Control of Gastric Acidity in Peptic Ulcer, *Lancet* **2** 881, 1939

167 Ronald, J. Value of Therapeutic Measures in Duodenal Ulceration, *Brit M J* **2** 1033, 1939

168 Steigmann, F., and Fantus, B. Acidity Modification Therapy in Peptic Ulcer, *Am J Digest Dis* **7** 197, 1940

169 Kirsner, J. B., and Palmer, W. L. The Effect of Various Antacids on the Hydrogen-Ion Concentration of the Gastric Contents, *Am J Digest Dis* **7** 85, 1940

bined use of atropine and calcium carbonate. They believe that the effectiveness of atropine is apparently due to the resultant diminution in the amount of gastric secretion and the prolongation of gastric emptying time.

Deleterious effects of antacid therapy have long been recognized, and among them is the possible causation of renal stones by use of alkalis in the treatment of ulcer. An article by Kretschmer and Brown¹⁷⁰ indicates that stone formation in alkali-treated patients is only 1.8 per cent greater than in patients who do not receive antacid therapy. They consider this difference is insignificant and agree with the point of view that the specific cause of renal and ureteral stone is unknown. Such a statement, while true, does not take into account recent work, such as that of Higgins and Albright, on the dissolution of renal stones, and there is strong reason to believe that renal stones may be formed by excessive alkali therapy in a few patients who have preexisting renal damage. Eisele's¹⁷¹ studies in this connection are of interest. He points out the great increase of work on the part of the kidney, with particular relation to an increased urinary excretion of solids, under alkali therapy.

The efficacy of aluminum hydroxide gel preparations in controlling symptoms of ulcer and in promoting healing continues to be reported by various observers¹⁷². There seems to be almost unanimous agreement that colloidal aluminum hydroxide administered either periodically or by continuous drip in connection with other generally accepted measures is of real value. Whitcomb,^{172a} in comparing its use with that of a routine Sippy regimen, believes that it shortens hospitalization and gives more constant relief than that obtainable by other antacids. Emery and Rutherford^{172b} are in agreement and cite as evidence of this the fact

170 Kretschmer, H. L., and Brown, R. C. Do Alkalis Used in the Treatment of Peptic Ulcer Cause Kidney Stones? Study of 1,940 Cases, *J. A. M. A.* **113** 1471 (Oct. 14) 1939.

171 Eisele, C. W. Changes in Acid-Base Balance During Alkali Treatment for Peptic Ulcer. Clinical Analysis of Alkalosis in Twenty-Eight Patients, *Arch. Int. Med.* **63** 1048 (June) 1939.

172 (a) Whitcomb, B. B. Results from Colloidal Aluminum Hydroxide in Peptic Ulcer Therapy. An Eighteen Month Survey at the Hartford Hospital, *J. Connecticut M. Soc.* **3** 272, 1939. (b) Emery, E. S., and Rutherford, R. B. Further Studies on Treatment of Peptic Ulcer with Aluminum Hydroxide Gel, *New England J. Med.* **222** 205, 1940. (c) Woldman, E. E., and Polan, C. G. Value of Colloidal Aluminum Hydroxide in Treatment of Peptic Ulcer, *Am. J. M. Sc.* **198** 155, 1939. (d) Steigmann, F. Colloidal Aluminum Hydroxide "Continuous Drip" in the Treatment of Large Gastric Ulcers. The Therapeutic and Diagnostic Value of this Method, *Illinois M. J.* **76** 443, 1939. (e) Eads, J. T. Clinical Results from the Continuous Intra-Gastric Drip Using Colloidal Aluminum Hydroxide in the Treatment of Peptic Ulcer, *Am. J. Digest. Dis.* **7** 32, 1940.

that a group of patients previously intractable to other medical measures finally responded to prolonged administration of aluminum hydroxide. Use of the continuous drip method is still stressed by Woldman and others,^{172c} particularly for patients who are refractory to healing and who have severe pain at night. There is little doubt that the aluminum hydroxide gel preparations constitute a permanent addition to the drug therapy of ulcer, the only disadvantage of their use being the tendency of such preparations to form fecal impactions. In addition to their action as antacids, it should be pointed out that administration of these preparations is followed by no subsequent increase in gastric secretion, such as may be observed following the use of certain alkalis, and, as is pointed out by Komarov and Komarov,¹⁷³ their antipeptic action appears to be as important both in vivo and in vitro as their action on gastric acidity. Komarov and Krueger¹⁷⁴ suggest, on the basis of Pavlov pouch experiments, that the use of colloidal aluminum hydroxide gel not only diminishes peptic activity by direct contact with the gastric juice in the stomach but causes a simultaneous diminution of peptic activity in a separate Pavlov pouch.¹⁷⁴

The necessity for care in preventing the development of specific nutritional deficiencies during treatment of patients with peptic ulcer still needs to be stressed. Although it probably is of no etiologic importance, there is little doubt that many patients with ulcer are on diets seriously lacking in ascorbic acid, a point again emphasized by Warren, Pijoan and Emery.¹⁷⁵ Brown, Northrop and Metheny¹⁷⁶ report 3 cases of surgically treated ulcer, in all of which there were evidences of pellagra. It is obvious that such deficiencies should be not only recognized but thoroughly treated before abandonment of medical measures.

There seems to be no real lack of agreement as to the indications for surgical treatment of peptic ulcer. Modifications in technic are relatively unimportant, and the increasing and probably justifiable popularity of subtotal gastrectomy as a proper operative procedure when operation is indicated seems to be established on firm grounds. That subtotal gastrectomy offers the final surgical solution of the ulcer problem is still open to some doubt, although it undoubtedly represents

173 Komarov, S. A., and Komarov, O. The Precipitability of Pepsin by Colloidal Aluminum Hydroxide, *Am J Digest Dis* **7** 166, 1940.

174 Komarov, S. A., and Krueger, L. The Effect of Aluminum Hydroxide Gel on Gastric Secretion in the Dog, *Am J Digest Dis* **7** 190, 1940.

175 Warren, H. A., Pijoan, M., and Emery, E. S., Jr. Ascorbic Acid Requirements in Patients with Peptic Ulcer, *New England J Med* **220** 1061, 1939.

176 Brown, H. K., Northrop, N. W., and Metheny, D. Peptic Ulcer and Pellagra. Report of Three Surgical Cases, *Northwest Med* **39** 101, 1940.

the most satisfactory approach as yet evolved. The comment of Knapper¹⁷⁷ is salutary. In a follow-up report on the surgical treatment of patients with duodenal ulcer he comments on the apparently successful results obtained but adds: "Since an interval of from 1 to 7 years does not permit a definite evaluation of the surgical results, the author intends to repeat the follow-up examinations after a few years." Such a point of view is distinctly healthy and indicates an honest skepticism of results which might be copied by many overenthusiastic surgeons. Finsterer¹⁷⁸ discusses the diagnosis and surgical treatment of juxta-cardiac gastric ulcers in an article on the diagnostic and therapeutic difficulties associated with these lesions, which are fortunately rather rare.

The problem of gastrojejunal ulcer and gastrojejunocolic fistula is a serious one, and articles by Finsterer¹⁷⁹ and Walters and Clagett¹⁸⁰ illustrate the hazards, as well as the rationale, of surgical intervention for these distressing complications of primary gastric operations. As Walters and Clagett point out, diagnosis is usually not difficult, although it is not always possible to obtain precise roentgen evidence of the existence of the lesion. Evaluation of recurrent symptoms and knowledge of the previous gastric surgical procedures are nearly always adequate for diagnosis. A careful study of these articles is of importance to the internist as well as to those interested in gastric surgery. The fact that gastrojejunal ulcers rarely develop after an anterior gastro-enterostomy is important. McPeak¹⁸¹ describes 2 cases of benign duodenocolic fistulas, which are of interest as medical curiosities, there being only 2 other possible cases in the literature at present. The diagnosis may be missed if roentgen examination is limited to study after a barium sulfate meal, the condition in this respect resembling gastro-jejunocolic fistulas, which frequently are demonstrated only after a barium sulfate enema.

The success of gastric surgical procedures frequently depends on detailed attention to postoperative nutritional needs, a point that is becoming more universally recognized by both surgeons and internists.

177 Knapper, C. Results of Modern Surgical Treatment of Ventricular (Duodenal) Ulcer, *Nederl tijdschr v geneesk* **83** 2058, 1939.

178 Finsterer, H. Juxta-cardiac Gastric Ulcer, *Wien klin Wchnschr* **52** 394, 1939.

179 Finsterer, H. Recurrent Peptic Ulcers of Jejunum and Surgically Incurable Ulcers, *Wien Arch f inn Med* **33** 296, 1940.

180 Walters, W., and Clagett, O. T. Gastrojejunal Ulcer. A Study of One Hundred and Fifty-Five Cases, *Am J Surg* **46** 83, 1939, Gastrojejunocolic Ulcer and Fistula, *ibid* **46** 94, 1939.

181 McPeak, C. N. Benign Duodenal-Colic Fistula, *Radiology* **34** 343, 1940.

Stengel and Ravdin¹⁸² describe the maintenance of nutrition in surgical patients and append a description of the orojejunal method of feeding. Their article is of technical as well as of practical interest as a contribution to postoperative care. An interesting observation in this regard is that of Dennis,¹⁸³ who demonstrated by microscopic studies that definite injury to the mucosa of the entire jejunum and ileum can result from instillation of distilled water. The mucosa of this part of the alimentary tract normally is never exposed to hypotonic solutions, and their use under artificial conditions is not justified. These observations demonstrate the necessity for caution in using distilled water rather than isotonic solutions for irrigations of the small bowel as a clinical measure.

The question of hemorrhage in relation to peptic ulcer continues to attract considerable attention. A review of the entire subject of gastrointestinal hemorrhage by Eusterman and Morlock¹⁸⁴ presents an excellent summary of the subject, particularly from the point of view of the actual causes of hematemesis. In addition, these authors call attention to the importance of bleeding from otherwise symptomless lesions, such as duodenal ulcers, or from any of the other several causes of bleeding of the upper part of the gastrointestinal tract. They indicate the need for serious study of this particular phase of the problem in the following statement: "Whether the absence of pain is due to individual nonsensitivity or to certain anatomic and physiologic factors, such as the depth of the lesion, the degree of resulting visceral dysfunction, the extent of direct involvement of nerves or peritoneal tissue, or to a combination of these factors, has not been definitely determined." They also draw attention to the role played by unusual physical or mental stress in precipitating these silent hemorrhages. Such a consideration is known to be of importance, but additional evidence for it is presented by Davies and Wilson¹⁸⁵ and by Melton.¹⁸⁶ The former authors investigated a group of 75 patients recovering from acute perforations or from attacks of massive hemorrhage, and stress the fact that episodes of unusual emotional tension immediately preceded these complications in four fifths of the patients. Melton reports what appears to be the

182 Stengel, A., Jr., and Ravdin, I. S. Maintenance of Nutrition in Surgical Patients with Description of Orojejunal Method of Feeding, *Surgery* **6** 511, 1939.

183 Dennis, C. Injury to the Ileal Mucosa by Contact with Distilled Water, *Am J Physiol* **129** 171, 1940.

184 Eusterman, G. B., and Morlock, C. G. Gastrointestinal Hemorrhage from Otherwise Symptomless Lesions with Special Reference to Duodenal Ulcer, *Am J Digest Dis* **6** 647, 1939.

185 Davies, D. T., and Wilson, A. T. M. Personal and Clinical History in Hematemesis and Perforation, *Lancet* **2** 723, 1939.

186 Melton, G. Hematemesis and the War, *Lancet* **1** 316, 1940.

direct effect of war strain in England as experienced in a single hospital, the incidence of admissions due to gross hemorrhage or perforation from ulcer actually doubling in the four months after the outbreak of hostilities over that noted in the preceding eight months

The incidence and mortality of massive hemorrhage continue to be sources of interest and of statistical reports,¹⁸⁷ of which only general mention can be made in this review. There is general agreement that mortality from this complication increases rapidly after the middle of the fifth decade of life and that medical treatment is indicated, with rare exceptions. The adoption of appropriate medical measures for patients under the age of 45 appears to reduce the mortality to an almost negligible figure, and Meulengracht's latest report,^{187d} of 10 deaths in a series of 491 patients with bleeding ulcers, is a very striking one. All agree that surgical intervention, either in the form of subtotal gastric resection or by transduodenal ligation of the bleeding vessel, should be resorted to only for patients in the older age groups and as an exceptional maneuver. The inclusion or exclusion of selected material still makes any critical analysis of statistical studies extremely difficult, but the preceding conclusions seem amply justified and are agreed to by most authors.

As to the details of medical treatment, there are naturally differences of opinion. With few exceptions, current articles agree that immediate feeding of a carefully prepared diet has no deleterious effects and is probably associated with real benefit to the patient from the point of view of shortening convalescence in the hospital and the period of recovery from the posthemorrhagic anemia as well as that of a possible immediate effect on the cessation of the hemorrhage. It is somewhat surprising to find that physicians like Andresen^{187c} fear the use of properly administered transfusions as an almost routine measure in the treatment of massive gastric hemorrhage. Almost all careful observers agree that there is no appreciable rise in blood pressure after a transfusion given slowly by the gravity method and that such a procedure is

187 (a) Blackford, J. M., and Cole, W. S. Massive Hemorrhage from Peptic Ulcer. A Study Based on Vital Statistics of the City of Seattle During Four Years and Personal Experience Based on Private Practice, *Am J Digest Dis* 6 637, 1939. (b) Graham, J. G., Alexander, J. C., and Kerr, J. D. O. Hemorrhage in Peptic Ulcer. Review of Two Hundred and Forty-One Consecutive Cases, *Lancet* 2 727, 1939. (c) Andresen, A. F. R. Results of Treatment of Massive Gastric Hemorrhage, *Am J Digest Dis* 6 641, 1939. (d) Meulengracht, E. Medical Treatment of Peptic Ulcer and Its Complications, *Brit M J* 2 321, 1939. (e) Holman, C. W. Severe Hemorrhage in Gastric and in Duodenal Ulcer. A Study of Ninety Cases, *Arch Surg* 40 150 (Jan) 1940. (f) Lanphere, G. H. Recent Advances in the Treatment of Hematemesis and Melena, *California & West Med* 52 59, 1940. (g) Jones, F. A. Hematemesis and Melena. Observations on the Use of Continuous Drip Transfusion, *Brit M J* 1 915, 1939.

important, with its actual contribution of hemoglobin, plasma protein and prothrombin as well as its immediate effect on the restoration of blood volume

Regeneration of blood and hemoglobin after massive hemorrhage appears to be determined in most instances by the degree of the anemia at the moment. It is of interest that two independent observers conclude that the rate of recovery from anemia may be nearly independent of the administration of food and iron. Graham, Alexander and Kerr^{187b} noted a remarkable recovery of hemoglobin following a single massive hemorrhage without administration of iron, and Lyons and Brenner¹⁸⁸ observed that the rate of regeneration was fully as good in cases of bleeding treated by a strict Sippy regimen as that reported for cases in which a liberal puréed diet and iron had been employed. Transfusions seemed to have no effect on the rate of erythropoiesis.

In referring to the generally recognized salt and water requirements after massive hemorrhage, Jones¹⁸⁹ suggests that the dehydration observed in such cases may be due not only to loss of fluid and subsequent insufficient fluid intake but in part to forced diuresis resulting from increased excretion of urea. The existence of marked azotemia following massive hemorrhage has been attested to by various authors since its original description by Christianson and Longinetti, but this factor has not been particularly recognized as of possible importance in stimulating diuresis and thereby increasing dehydration following hemorrhage. The exact mechanism responsible for producing such azotemia is still open to some doubt, and the results of studies reported by various writers¹⁹⁰ are not in entire agreement. That the rise in blood urea is due in part to actual absorption of nitrogenous material from decomposition of blood in the intestinal tract is fairly generally accepted. The statement that it is not associated with impairment of renal function, even though transient (Schiff and his collaborators^{190a}), is open to real doubt. There is also no general agreement as to the exact prognostic significance of an

188 Lyons, R. H., and Brenner, C. Erythropoiesis Following Bleeding Peptic Ulcer, *Am J M Sc* **198** 942, 1939

189 Jones, F. A. Hematemesis and Melena. Observations on Salt and Water Requirements, *Brit M J* **2** 332, 1939

190 (a) Schiff, L., and Stevens, R. J. Elevation of Urea Nitrogen Content of the Blood Following Hematemesis or Melena, *Arch Int Med* **64** 1239 (Dec) 1939. (b) Stevens, R. J., Schiff, L., Lublin, A., and Garber, E. S. Renal Function and Azotemia Following Hematemesis, *J Clin Investigation* **19** 233, 1940. (c) Demole, M., and Neeser, J. Hyperazotemia in Digestive Hemorrhage, *Gastroenterologia* **64** 208, 1939. (d) Black, D., and Leese, A. Nitrogen and Chloride Metabolism in Gastro-Duodenal Hemorrhage, *Quart J Med* **9** 129, 1940. (e) Kaump, D. H., and Parsons, J. C. Extrarenal Azotemia in Gastro-intestinal Hemorrhage. I General and Clinical Considerations, *Am J Digest Dis* **7** 189, 1940, II Experimental Observations, *ibid* **7** 191, 1940

elevation of blood urea nitrogen Schiff and others affirm that repeated estimations of blood urea in cases of hematemesis are indicated because of their prognostic significance and as an aid to therapeutic management, while others, e g, Demole and Neeser,^{190c} doubt that any such clinical significance is attached to the values. In all probability it will still be proper to consider the evidences of nitrogen retention associated with massive gastrointestinal hemorrhage as an interesting expression of physiologic disturbance rather than as a guide to clinical decisions or therapeutic measures.

An article by Daniel and Egan¹⁹¹ is of incidental interest in this regard. These authors determined the approximate quantity of blood necessary to produce a tarry stool and conclude that the presence of at least 50 to 80 cc of blood is needed in the gastrointestinal tract for the occurrence of such a phenomenon.

Many articles appeared during the year discussing acute perforation in cases of peptic ulcer. Most of them are surgical and contribute nothing new to an understanding of this particular complication of ulcer. Almost all writers agree that immediate operation is indicated, although it is known that occasionally conservative measures are permissible, particularly if diagnosis is too long deferred. Simple closure remains the treatment of choice according to most writers, with the exception of a few of the more radical surgeons, especially those on the Continent.

Surgical mortality from this condition is still high, owing in large part to delayed or mistaken diagnoses. For this reason one cannot emphasize too strongly the fundamental importance attaching to an early diagnosis of the condition by internists, who are for the most part concerned with the treatment of peptic ulcer.

A historically interesting summary of changes in age incidence and sex distribution of perforated peptic ulcer is presented by Jennings.¹⁹² The author provides a rather unusual summary of changes that have apparently taken place in the past one hundred and fifty years in England, Germany, France, Scandinavia and the English-speaking countries. As good a statistical study as any is that presented by Odom and DeBakey,¹⁹³ who report an incidence of approximately 8 per cent of perforations in 2,600 patients with peptic ulcer admitted to the hospital wards during a ten year period. Reference to the majority of these articles is unnecessary for this review, as they are chiefly of surgical interest.

191 Daniel, W. A., Jr. and Egan, S. The Quantity of Blood Required to Produce a Tarry Stool, *J. A. M. A.* **113** 2232 (Dec. 16) 1939.

192 Jennings, D. Perforated Peptic Ulcer. Changes in Age Incidence and Sex Distribution in Last One Hundred and Fifty Years, *Lancet* **1** 395, 1940.

193 Odom, C. B., and DeBakey, M. Acute Perforated Gastric and Duodenal Ulcer, *New Orleans M. & S. J.* **92** 359, 1940.

Gjankovic¹⁹⁴ made an interesting observation on covered perforation of gastric and duodenal ulcer. The author reviews the literature on closed perforations of peptic ulcer and reveals that he encountered this condition in 10 per cent of his own operative cases. He admits that the prognosis of covered perforations is generally favorable and that spontaneous cure is possible but quite properly holds that surgical intervention is nearly always indicated, in spite of the possibility of such spontaneous protective measures.

The possibility of an associated hemorrhage with perforation is pointed out by several authors.¹⁹⁵ The important dangers and the treatment of peptic ulcers perforating into the pancreas are pointed out by Horsley.¹⁹⁶ Hadley¹⁹⁷ reports an unusual form of perforation of the stomach following antisyphilitic treatment of a gastric gumma, perforation being evidenced by roentgen examination. Another fortunately rare occurrence is that noted by Law,¹⁹⁸ who reports 2 cases of perforated jejunal ulcer subsequent to partial gastrectomy. Still another most unusual result of perforation of a duodenal ulcer is that reported by Gottlieb,¹⁹⁹ in which roentgen examination revealed the presence of gas in the biliary ducts. The preoperative diagnosis was duodenobiliary fistula, and operation and subsequent autopsy showed a duodenal ulcer of long standing with perforation clearly into the gallbladder.

Of diagnostic significance is the report of Feldman²⁰⁰ on the effect of peptic ulcer activity on cholecystography. It has been repeatedly noted that apparently falsely positive cholecystograms are occasionally obtained in the presence of peptic ulcer without true disease of the gallbladder. Feldman reports the results of studies made in 115 cases of peptic ulcer. Ten per cent of the patients showed abnormal filling of the gallbladder, and more than 25 per cent appeared to have sluggish or noncontracting gallbladders. In 5 per cent of the 115 cases of ulcer, there were associated actual gallstones, an association which frequently makes accurate diagnosis difficult.

194 Gjankovic, H. Covered Perforation of Gastric and Duodenal Ulcer, *Presse med* **47** 1263, 1939.

195 Winters, W. L., and Egan, S. Incidence of Hemorrhage Occurring with Perforation in Peptic Ulcer, *J A M A* **113** 2199 (Dec 16) 1939. Meyer, H. W. Perforation of the Gastrointestinal Tract, *Ann Surg* **112** 37, 1940.

196 Horsley, J. S. Peptic Ulcers Perforating into the Pancreas, *Ann Surg* **110** 606, 1939.

197 Hadley, H. G. Perforation of Stomach Due to Syphilis, *Radiology* **35** 86, 1940.

198 Law, W. A. Perforated Jejunal Ulcer Following Partial Gastrectomy, *Brit M J* **1** 844, 1940.

199 Gottlieb, C. Visualization of Biliary Ducts by Means of Gas Following Spontaneous Duodenal Ulcer Rupture, *Radiology* **33** 470, 1939.

200 Feldman, M. Effect of Peptic Ulcer in Cholecystography, *Am J Roentgenol* **43** 58, 1940.

Small Intestine—Reports on anatomic abnormalities of the duodenum are encountered as usual. Among them, the report by Feldman and Morrison²⁰¹ of 14 cases of inverted duodenum is of some interest. The significance of megaduodenum and "duodenal obstruction" is carefully discussed by Sturtevant²⁰². He reviews thoroughly the various interpretations of this not uncommon condition, and perusal of his article reveals a sensible attitude toward the clinical significance and the therapeutic implications of this condition. He describes the characteristic roentgen picture leading to a diagnosis of obstruction but adds that even the presence of apparently typical roentgen criteria is not always conclusive. He states that true duodenal obstruction with dilatation is an entity, but a distinctly rare one. So much has been written on the subject that is based largely on rather loose clinical impressions that Sturtevant's article is of real value.

As a rule, it is unwise to attribute much clinical significance to accidental demonstrations of duodenal diverticula. Occasionally, however, they may be the cause of important clinical symptoms and may even lead to perforation, with serious results. The case reported by Boland²⁰³ is worthy of note, particularly because of the rarity with which symptoms are encountered as a result of this uncommon abnormality. Two other rare instances of fatal abdominal emergencies secondary to perforation are reported by Roach²⁰⁴ and by Ottenheimer and Gilman²⁰⁵. The case reported by Roach was one of fatal hematemesis caused by rupture of an abdominal aortic aneurysm into the third portion of the duodenum. Ottenheimer and Gilman report a case of traumatic rupture into the retroperitoneal portion of the duodenum following injury to the right side of the chest and the abdomen, an extremely rare condition. The few reports on primary malignant tumor of the duodenum that have appeared during the current year serve only to testify to the rarity of this disease.

The frequency of primary jejunal pathologic change was indicated in the statistical study of Browne and McHardy,²⁰⁶ based on a statistical

201 Feldman, M., and Morrison, T. H. Inverted Duodenum. Its Clinical Significance with Report of Fourteen Cases, *Am J M Sc* **20** 69, 1940.

202 Sturtevant, M. Megaduodenum and Duodenal Obstruction. Criteria for Diagnosis, *Radiology* **33** 185, 1939.

203 Boland, F. K., Jr. Acute Perforated Duodenal Diverticulum, *Surgery* **6** 65, 1939.

204 Roach, R. D. Rare Cause of Fatal Hematemesis, *Canad M A J* **41** 173, 1939.

205 Ottenheimer, E. J., and Gilman, R. L. Rupture of the Retroperitoneal Duodenum, *New England J Med* **222** 251, 1940.

206 Browne, D. C., and McHardy, G. Primary Jejunal Pathology. *J A M A* to be published.

examination of nearly 8,000 autopsies. They encountered a single example each of traumatic regional enteritis and intussusception, 16 diverticula, 4 perforated ulcers and 11 neoplasms, of which 7 were benign and 4 malignant. These authors, together with Kiefer,²⁰⁷ present excellent routine summaries of the clinical aspects of disorders of the jejunum and the small bowel and indicate the increasing interest in diagnosis of disease of a portion of the digestive tract previously avoided because of technical diagnostic difficulties. With the exception of disorders causing diarrhea, the symptoms of jejunal and ileal disease are fundamentally those of partial or complete obstruction, and too much attention cannot be paid to acquisition of a detailed history as to the occurrence of umbilical pain or peristaltic discomfort if an early diagnosis of jejunal and ileal lesions is to be expected.

An excellent résumé of the subject of intestinal obstruction due to intraluminal foreign bodies is that by Storck, Rothschild and Ochsner.²⁰⁸ These authors review 875 cases of intestinal obstruction, exclusive of hernia, neoplasm and peritonitis. Obstruction in almost 6 per cent of these cases was due to foreign bodies, including gallstones, intestinal parasites, bezoars and a miscellaneous group of others. The clinical description included in the article is well worthy of study, and the large variety of foreign bodies mentioned seems to include almost all the possibilities.

Numerous articles on intestinal obstruction due to gallstones bear witness to the relative frequency of this complication of disease of the gallbladder. Snodgrass²⁰⁹ adds nonabsorbable suture material to the list of foreign bodies capable of causing intestinal obstruction. His case is of interest because of the fact that material had been introduced into the abdomen twenty-four years previously.

It has long been known that bran may act as a real irritant to the gastrointestinal tract. A report by Fantus and Kopstein²¹⁰ indicates that its use may be associated with the production of intestinal obstruction in the presence of predisposing organic disease, and these authors properly advise against its use when intestinal ulceration, stenosis or adhesions are known to be present.

The number of reports on benign and malignant tumors of the small bowel is steadily growing and indicates a rapidly accumulating interest

207 Kiefer, E. D. Clinical Aspects of Chronic Disorders of the Small Intestine, *J. A. M. A.* **113** 1546 (Oct 21) 1939.

208 Storck, A., Rothschild, J. E., and Ochsner, A. Intestinal Obstruction Due to Intraluminal Foreign Bodies, *Ann. Surg.* **109** 844, 1939.

209 Snodgrass, T. J. Acute Intestinal Obstruction Caused by Nonabsorbable Suture Material, *Surgery* **6** 437, 1939.

210 Fantus, B., and Kopstein, G. Does Bran Produce Intestinal Obstruction? *Am. J. Digest. Dis.* **7** 60, 1940.

and skill in dealing with disease of the small intestine. Among the best reports of malignant tumors of the small bowel are those by Medinger²¹¹ and Cohn, and Landy and Richter.²¹² Several articles record the finding of argentaffin tumors of the appendix and small bowel, the most complete report being that of Porter and Whelan.²¹³

Reports, such as that by Pachman,²¹⁴ on such surgical rarities as enterogenous cysts are of interest merely for purposes of inclusion among potential causes of intestinal obstruction. Mere mention of innumerable other causes of intestinal obstruction will suffice, as individual reports add little that is new. Volvulus, obstruction secondary to the Baldy-Webster type of uterine suspension, torsion of the appendices epiploicae, intussusception following attacks of Henoch's purpura, Meckel's diverticulum, hyperplastic tuberculosis of the ileum, intestinal intussusception in infants and even extrinsic antenatal intestinal obstruction of the ileum all receive attention in a large series of articles, which are of interest merely for purposes of classification and surgical technique.

The entire question of intestinal obstruction, regardless of its underlying cause, is one that fundamentally involves surgical consideration. To internists, particularly those interested in gastroenterology, a diagnostic interest in the factors underlying the condition and a more complete understanding of the physiologic disturbances incident to it warrant inclusion of several articles that are primarily of surgical interest. Orr²¹⁵ records 2 cases of intestinal obstruction due to mechanical injury to the spine which was treated conservatively as paralytic ileus. The chief importance of the report is that it points out the necessity for establishing the cause of abdominal distention in relation to orthopedic conditions, among others. The discomfort of a distended abdomen beneath such a cast as might be applied to a patient suffering from spinal injury may be falsely interpreted as due to paralytic ileus, with delay in treatment and perhaps a fatal outcome. The occurrence of severe colicky pain in such a patient is indication for removal of the cast and further complete examination, to exclude actual obstruction.

211 Medinger, F. G. Malignant Tumors of Small Intestine. Study of Their Incidence and Diagnostic Characteristics, *Surg., Gynec. & Obst.* **69** 299, 1939.

212 Cohn, S., Landy, J. A., and Richter, M. Tumors of Small Intestine, *Arch. Surg.* **39** 647 (Oct.) 1939.

213 Porter, J. E., and Whelan, C. S. Argentaffin Tumors. Report of Eighty-Four Cases, Three with Metastases, *Am. J. Cancer* **36** 343, 1939.

214 Pachman, D. J. Enterogenous Intramural Cysts of Intestines, *Am. J. Dis. Child* **58** 485 (Sept.) 1939.

215 Orr, T. G. Paralytic Ileus and Intestinal Obstruction Complicating Skeletal Injuries, *South. M. J.* **32** 508, 1939.

Physiologic disturbances that may occur as a result of intestinal obstruction have been further studied by Gendel and Fine,²¹⁶ who record the result of experimental acute intestinal obstruction in dogs on blood plasma volume. They stress the importance of early progressive loss of blood plasma, which may reach 36 per cent within four to six hours, with a loss of plasma volume of as high as 55 per cent within twenty-four hours after production of the obstruction. Such a loss of plasma, which is equivalent to about 3 per cent of the body weight, is more than sufficient in itself to cause death and occurs particularly in cases in which strangulation is added to obstruction. Hematocrit readings, with direct evidence of the loss of plasma volume, are apparently more accurate as regards the patient's condition than are blood pressure readings. Administration of adequate quantities of plasma by the intravenous route is recommended by these authors, with sound reasons. They also show that the survival time of animals with obstruction and gaseous distention of the small intestine is inversely proportional to the level of the pressure in the lumen of the bowel. Such experimental data provide a reasonable basis for the necessary details of successful treatment.

Excellent summaries of actual results in treating acute mechanical obstruction of the small intestine are provided in the articles of McKittrick and Sarris,²¹⁷ Wangensteen,²¹⁸ and Lupton,²¹⁹ all of whom stress the importance of decompression measures and replacement of fluids, electrolytes and plasma volume. Wangensteen emphasizes the importance of fluid loss in this condition in an estimate that approximately 7,000 cc of fluid may enter the intestinal canal in the form of digestive juices. The indications for and limitations of decompression treatment by the use of the Miller-Abbott tube or the Wangensteen apparatus are well discussed by Rea,²²⁰ who, with others, points out the dangers of failure to differentiate between paralytic ileus and acute mechanical obstruction. The use of lumbar block induced with procaine hydrochloride as a conservative method of treating acute ileus is recorded

216 Gendel, S, and Fine, J. Effect of Acute Intestinal Obstruction on Blood and Plasma Volumes, *Ann Surg* **110** 25, 1939. Fine, J, Rosenfeld, L, and Gendel, S. Role of Nervous System in Acute Intestinal Obstruction. Experimental Investigation, *ibid* **110** 411, 1939.

217 McKittrick, L S, and Sarris, S P. Acute Mechanical Obstruction of Small Bowel. Its Diagnosis and Treatment, *New England J Med* **222** 611, 1940.

218 Wangensteen, O H. Experimental and Clinical Observations Relating to the Management of Acute Bowel Obstruction, *Ann Int Med* **13** 987, 1939.

219 Lupton, C H. Intestinal Obstruction, *Virginia M Monthly* **66** 610, 1939.

220 Rea, C E. Diagnosis and Treatment of Small Bowel Obstruction, *Am J Surg* **46** 604, 1939.

by Novikov.²²¹ In more than half of a group of 140 patients admitted to the surgical clinic with acute intestinal obstruction procaine hydrochloride was injected into the right or the left iliac fossa, and in nearly two thirds of the cases procaine block alone resulted in diminution of pain passage of flatus and a copious bowel movement. In a third of the patients so treated the maneuver relieved pain and caused some passage of flatus but no stool. Novikov advocates the method as offering a possibility of preoperative recognition and of effective treatment of functional ileus. He also believes it may prevent the transition of functional ileus into mechanical ileus. It is obvious, however, that again careful clinical judgment is necessary to differentiate between conditions definitely requiring immediate operation and those which will permit a reasonable delay. An unusual form of treatment of mechanical obstruction of the small intestine is that reported by Smith,²²² who presents the results of treatment by hyperthermia of 2 patients with obstruction of the small bowel secondary to gonorrheal adnexitis. Because of the danger of dehydration chloride depletion and alkalosis inherent both in fever therapy and in intestinal obstruction, great caution is obviously necessary but the report is of interest because of the specific nature of treatment for one of the known causes of intestinal obstruction.

Further evidence of the diagnostic value of roentgen studies after intubation of the small intestine in cases of partially obstructive lesions is presented by Boone,²²³ who used the Miller-Abbott tube in this connection. Findings suggesting incomplete obstruction are permanent arrest in the passage of the balloon, unusual regurgitation of an injected barium mixture and persistent narrowing of the intestine distal to the shadow of the barium. With sufficient experience, one can undoubtedly localize and demonstrate pathologic processes in the bowel or its vicinity capable of causing intermittent or permanent narrowing.

Large Intestine—As with conditions involving the small bowel, reports of congenital abnormalities of the colon are of interest largely because they call attention to already recognized but relatively uncommon conditions. A few articles concerned with megacolon will be mentioned. Tiffin, Chandler and Faber²²⁴ report a case of megacolon in which the sigmoid flexure was of normal caliber but the entire colon above that

221 Novikov, G. M. Procaine Hydrochloride Block in Acute Ileus, *Vestnik khir* 58: 506, 1939.

222 Smith, B. A., Jr. Fever Therapy in Treatment of Mechanical Intestinal Obstruction Due to Pelvic Inflammatory Disease, *Surgery* 7: 61, 1940.

223 Boone, T. H. Intubation of Small Intestine. Demonstration and Localization of Partially Obstructive Lesions, *Lancet* 1: 7, 1940.

224 Tiffin, M. E., Chandler, L. R., and Faber, H. K. Localized Abscess of the Ganglion Cells of the Myenteric Plexus in Congenital Megacolon, *Am J Dis Child* 59: 1071 (May) 1940.

segment was abnormally dilated and hypertrophied. Administration of cholinergic drugs caused contraction of the bowel without propulsion of its contents, and sympathectomy did not influence the condition favorably. Histologic examination of the intestinal wall revealed that the cells of Auerbach's plexus were normal in number and appearance throughout the hypertrophied and dilated portion of the bowel but were greatly diminished or absent in the nondilated sigmoid flexure of the colon. The authors suggest that the condition appears to be closely related to that known to exist in the presence of cardiospasm or achalasia of the esophagus, in which absence of the peripheral neurons of the parasympathetic system has been observed. In this connection the work of Etzel, reviewed by Silva and de Paula,²²⁵ is of interest, although in no way conclusive. Etzel believes that the destruction of Auerbach's plexus seen in cases of cardiospasm and megacolon is brought about by a deficiency in the vitamin B content of the diet. He found that practically all of his Italian patients with megacolon and megaesophagus came from a district where pellagra and dietary deficiencies are known to be of frequent occurrence. Law²²⁶ describes the successful treatment of 6 children suffering from megacolon with acetylbetamethylcholine bromide. Two of these patients were able to discontinue the use of the drug after three and nine months, respectively. Such results, as well as those reported by Telford and Simmons²²⁷ on successful treatment of megacolon in children in 7 cases and of megaesophagus in 1 case by the use of spinal anesthesia, still further contribute to the accumulating evidence of the fundamental role played by disturbances of the autonomic nervous system in these conditions.

To those interested in the diagnosis and treatment of congenital anomalies of the anus and rectum, attention may be directed to a fairly complete review of the subject by Crowell and Dulin.²²⁸

Diverticulosis of the colon, because of its frequent occurrence, continues to attract attention. An authoritative article by Buie²²⁹ gives a complete description of colonic diverticula, including a description of prenatal and postnatal manifestations of the condition, incidence, anatomic situation, pathologic picture, relation of the disease to malignant

225 Silva, G. S., and de Paula, E. Chronic Vitamin B₁ Deficiency in the Etiology of Megoesophagus and Megacolon, editorial, *Am J Digest Dis* **7** 184, 1940.

226 Law, J. L. The Treatment of Megacolon with Parasympathetic Drugs, *J A M A* **114** 2537 (June 29) 1940.

227 Telford, E. D., and Simmons, H. T. Treatment of Gastrointestinal Achalasia by Spinal Anesthesia, *Brit M J* **2** 1224, 1939.

228 Crowell, E. A., and Dulin, J. W. Congenital Anomalies of the Anus and Rectum, *Surgery* **7** 529, 1940.

229 Buie, L. A. Diverticula of the Colon, *New England J Med* **221** 593, 1939.

tumor of the colon and treatment. The author discusses rather fully the medical and the surgical treatment of this condition stating that the necessity for the latter arises in about 10 per cent of all cases. A particularly accurate and valuable description is given of the sigmoidoscopic findings associated with sigmoidal diverticulitis. He stresses the importance of suspecting the presence of malignant changes in patients with diverticulitis of the sigmoid flexure, with the necessity for complete and repeated studies to determine the benignity of the lesion. It might be added that there is no particular evidence that malignant disease is secondary to diverticulitis, the association being no more common than is to be noted in the average run of patients. Brown²³⁰ stresses the frequency with which diverticulosis can be demonstrated, stating that it is present in about 5 per cent of persons 40 years old or older. The number of cases in which diverticulitis will sooner or later develop and in which operation will eventually be required is unpredictable. He stresses the rapidity with which symptoms requiring operation may develop in patients in whom symptomless diverticulosis has been present for a long time but agrees with other writers that medical treatment is entirely adequate in all but a small percentage of cases. The importance of acute perforative diverticulitis is brought out in his article and in that by Bearse,²³¹ and a rather unusual complication, pylephlebitis, the original cause of which is not frequently suspected, is reported by Pepper.²³²

Considerable attention is properly paid to the subject of polyps of the colon and rectum. A careful statistical and pathologic study of this condition is presented by Swinton and Warren²³³ on the basis of observations in 156 patients and an analysis of more than 800 cases in which operation for carcinoma of the colon and rectum was done. They point out that the actual incidence of polypoid disease of the colon and rectum is not known but correctly believe that it is much more common than has been recognized. Certain important facts are discussed. Nearly three fourths of the polyps in this series could be visualized with a sigmoidoscope, a fact leaving little excuse for failure to examine instrumentally all patients with rectal bleeding. This particular point cannot be stressed too frequently or too earnestly. Another important observation in this series is that about one third of the patients had multiple

230 Brown, P. W. The Treatment and Prognosis of Diverticulitis of the Colon, *Am J Surg* **46** 162, 1939.

231 Bearse, C. Acute Perforative Diverticulitis of the Colon in Young Persons, *J A M A* **113** 1720 (Nov 4) 1939.

232 Pepper, O. H. P. Diverticulitis of the Colon, *Pennsylvania M J* **42** 1043, 1939.

233 Swinton, N. W., and Warren, S. Polyps of the Colon and Rectum and Their Relation to Malignancy, *J A M A* **113** 1927 (Nov 25) 1939.

polypi Histologic examination of the material removed at operation showed all stages in the sequence of change from normal mucosa to adenocarcinoma One seventh of over 800 patients with cancer of the colon and rectum presented almost certain evidence of malignant degeneration from previously benign polypoid tumors The importance of these observations cannot be overestimated, although they are in no way new That a diagnosis of polyps may be made on the basis of symptoms in children is evident from the report of Kennedy²³⁴ on 42 instances of this condition in infants and children The chief symptoms and signs directing attention to the disease were the presence of fresh blood in the stools and a mass protruding from the anus An unusual example is the case report of a boy aged 7 years whose initial symptom, rectal bleeding, dated from the age of 3 months An interesting complication of the successful surgical treatment in this particular case was the development of spontaneous bleeding on the twenty-fifth postoperative day, due to prothrombin deficiency²³⁵

The importance of the relation between intestinal polyps and malignant disease is particularly well discussed by Coffey and Bargaen²³⁶ The article is well worth reading because of its completeness Among other interesting statistical facts is the statement that two thirds of a series of patients with multiple adenomatous polyps had carcinoma Additional evidence of the recognized tendency to malignant degeneration and the familial incidence of carcinoma is to be found in articles by Lockhart-Mummery and Dukes²³⁷ and McKenney²³⁸ The latter describes 4 siblings between the ages of 2 and 11 who had malignant degeneration from multiple polypi, and in the report by Lockhart-Mummery and Dukes a fairly complete study of the course of adenomatosis of the colon and rectum in ten families demonstrates convincingly the general familial character of the disease and its close relation to cancer, in a history that carried through several generations A very important part of the article by Coffey and Bargaen is the extremely careful description of polyposis arising as a complication of chronic ulcerative colitis Of the polyps noted in the course of ulcerative colitis, 56 per cent were

234 Kennedy, R L J Polyps of the Colon and Rectum in Infants and Children, *Proc Staff Meet, Mayo Clin* **15** 108, 1940

235 Dixon, C F, and Gregg, R O Management of Postoperative Intestinal Obstruction Complicated by Hemorrhage on the Basis of Prothrombin Deficiency, *Minnesota Med* **23** 169, 1940

236 Coffey, R J, and Bargaen, J A Intestinal Polyps Pathogenesis and Relation to Malignancy, *Surg, Gynec & Obst* **66** 136, 1939

237 Lockhart-Mummery, J P, and Dukes, C E Familial Adenomatosis of Colon and Rectum Its Relationship to Cancer, *Lancet* **2** 586, 1939

238 McKenney, D C Multiple Polyposis Congenital, Heredofamilial, Malignant, *Am J Surg* **46** 204, 1939

pseudoadenomatous, 21 per cent were adenomatous and 21 per cent were carcinomatous. The incidence of cancer is obviously smaller than that noted in cases of intestinal polyps not associated with chronic inflammation but represents an important figure. The seriousness of the condition is indicated by the fact that the surgical mortality in this last group was 66 per cent, owing undoubtedly to the associated presence of ulcerative colitis. Of additional interest is the fact that with improved medical treatment of this condition the incidence of polyposis was reduced from approximately 16 per cent to 10 per cent, although the accuracy of roentgen diagnosis had increased tremendously.

The treatment of intestinal polyps is obviously surgical, but the enthusiasm evinced by certain authors for fulguration through a sigmoidoscope (Hedin²³⁹ and Smith²⁴⁰) should not be taken to indicate that such a procedure is not without great risk except in the hands of very skilful operators.

Because of the appalling incidence of death from cancer of the rectum and colon, it is important to refer briefly to a number of articles directing attention to the diagnosis and treatment of this condition. The diagnosis should be made with much greater frequency by proper attention to easily elicited symptoms. Lahey²⁴¹ brings out this point very clearly in an analysis of a large group of cases. Histories taken in 300 proved cases of cancer, in which the tumors were equally divided in location between the right side of the colon, the left side of the colon and the rectum, showed that there was an alteration in intestinal function, abdominal cramps or abnormal stools in 97 per cent of the cases. The presence of abnormal stools was noted in 86 per cent of cases of cancer of the rectum and in nearly half of the cases of cancer of the left side of the colon but in less than 10 per cent of the cases in which there was involvement of the right side of the colon. Because of the almost certain influence of trauma, irritation and infection in predisposing to carcinomatous degeneration, the discovery of any of the aforementioned symptoms or of bleeding should lead to a most careful search for evidences of malignant disease. It is important to recognize that skilful and effective surgical measures are almost universally available in all important medical centers at present, and the denial of help until after obstructive symptoms have occurred, once a diagnosis has been established, is absolutely inexcusable, as has

239 Hedin, R. F. Polypoid Disease of the Colon. Anatomical Measurements of the Colon Including Description of a Colonscope, *Surgery* **6** 909, 1939.

240 Smith, N. D. The Diagnosis and Fulguration of Polyps in the Rectum and Sigmoid, *Proc. Staff Meet., Mayo Clin.* **15** 101, 1940.

241 Lahey, F. H. Neoplasms of Cecum and Ascending Colon, *Am. J. Surg.* **46** 3, 1939.

been pointed out in numerous authoritative articles by well known surgeons²⁴² One additional point of importance regarding the incidence of the condition, namely, the occurrence of cancer of the rectum and colon in young persons, is stressed by several writers,²⁴³ all of whom report the occurrence of this condition in groups of persons well under the so-called cancer age

Although radical surgical treatment of colonic and rectal malignant disease is the therapy of choice, it should not be forgotten that there is still a place for radiation therapy A full description of the possibilities of radiologic treatment of cancer of the rectum is given by Berven,²⁴⁴ who points out that preoperative roentgen treatment may be of real help in an attack on the undifferentiated types of cancer, particularly in cases of large disintegrating operable tumors Patients in whom only an incomplete removal is possible or who refuse surgical procedures should be given the benefit of radiation therapy, as should all inoperable patients whose general health permits Such treatment not infrequently provides an endurable existence for these patients for an appreciable period The author believes that anorectal carcinoma of the cutaneous type should first be treated radiologically He also points out that only during the last fifteen years has radiologic treatment been tested to any great extent and that with improved technic and instruments the benefits to be derived from this form of therapy still warrant considerable study An article by Meland²⁴⁵ is in accord with the foregoing comments, and in another report²⁴⁶ on carcinoma of the anus the same author discusses the symptomatology of this condition and brings out one important point which usually escapes accurate interpretation In several patients the presenting symptom was back-ache This is worthy of attention, as it is not too infrequent that dis-

242 Allen, A W, and Welch, C E Malignant Diseases of Colon Factors Influencing Operability, Morbidity and Mortality, *Am J Surg* **46** 171, 1939 Stone, H B, and McLanahan, S Carcinoma of the large Bowel Surgical Aspects, *J A M A* **113** 2282 (Dec 23) 1939 Ochsner, A, and DeBakey, M Operability, Morbidity and Mortality Factors in Carcinoma of the Colon, *Am J Surg* **46** 103, 1939 Rankin, F W, and Graham, A S Cancer of the Rectum and Rectosigmoid Diagnosis and Treatment, *ibid* **46** 18, 1939

243 Mayo, C W, and Madding, G F Carcinoma of Rectum and of Rectosigmoid in the Young, *Arch Surg* **40** 83 (Jan) 1940 Rosser, C, and Kerr, J G Cancer of the Rectum in Young Persons, *J A M A* **113** 1192 (Sept 23) 1939 Rawls, W B Carcinoma of the Colon Occurring in a Girl Thirteen Years Old, *New York State J Med* **40** 290, 1940

244 Berven, E Radiologic Treatment of Cancer of Rectum, *Acta radiol* **20** 373, 1939

245 Meland, O N What Can One Expect from Radiation in Carcinoma of Rectum and Anus? *California & West Med* **50** 403, 1939

246 Meland, O N Carcinoma of Anus, *Am J Roentgenol* **43** 706, 1940

eases at various levels of the gastrointestinal tract first give notice of their existence by symptoms strongly suggestive of disease of the vertebral column

Individual instances of unusual colonic tumors, such as simple lymphomas and neurogenic fibromas, are reported but are of interest only as rare findings. One form of rectal tumor, however, is worthy of note, namely, that secondary to injection treatments for hemorrhoids. Jackman²⁴⁷ reports 3 cases of submucosal tumor masses or rectal stricture subsequent to the use of oil base sclerosing preparations, which the author properly condemns. An unusual complication of cancer was that reported by Renander,²⁴⁸ who points out that when perforation occurs in association with cancer of the proximal part of the colon it usually breaks into the duodenum, with development of a duodenal-colic fistula, while distal colonic cancer, especially that in the region of the splenic flexure, usually produces a gastrocolic fistula. The author reports 2 cases of cancer of the descending colon perforating posteriorly and laterally into the retroperitoneal space and suggesting the diagnosis of perinephritic abscess. Nonmalignant, subparietal rupture of the intestine due to muscular effort is an unusual example of colonic disease, but MacMillan²⁴⁹ records 43 cases from the literature and 2 of his own. Although hernia was present in the majority of instances, in the author's own cases there was no herniation and no other injury of the abdominal wall, except that associated with muscular effort. The inclusion of a case report by Judd, Larsen and Tilden²⁵⁰ of linitis plastica of the colon is warranted because of the diffuse involvement that was found. The entire descending colon showed evidence of this condition, and the term "malignant fibrosis" was suggested as less apt to mislead the surgeon with a false sense of security when microscopic examination reveals only fibrous tissue. A most unusual cause of massive rectal bleeding is found in 2 case reports by Fleet²⁵¹ and Ewell and Jackson²⁵². Both describe the occurrence

247 Jackman, R. J. The Differential Diagnosis, Pathologic Aspects and Treatment of Rectal Tumors of Chemical Origin, *Proc. Staff Meet., Mayo Clin.* **15** 188, 1940.

248 Renander, A. Covered Perforations in Cancer of Colon, *Acta radiol.* **20** 257, 1939.

249 MacMillan, S. F. Subparietal Rupture of the Intestine Due to Muscular Effort. Report of Two Cases, *Ann. Surg.* **111** 49, 1940.

250 Judd, J. R., Larsen, N. P., and Tilden, I. L. Linitis Plastica of Colon, *Surgery* **6** 278, 1939.

251 Fleet, G. A. Misplaced Gastric Mucosa as a Cause of Massive Rectal Hemorrhage, *Canad. M. A. J.* **42** 216, 1940.

252 Ewell, G. H., and Jackson, R. H., Sr. Aberrant Gastric Mucosa in the Rectum with Ulceration and Hemorrhage, *Wisconsin M. J.* **38** 641, 1939.

of profuse rectal bleeding secondary to aberrant gastric mucosa in the rectum in children. Previous reports of this condition are not available in the literature.

The possibility of fecal impaction as a cause of serious symptoms is too frequently overlooked by clinicians trained in the diagnosis of more formidable conditions. It is of importance, therefore, to allude to such articles as that by Benson and Bargen,²⁵³ particularly because therapeutic measures, if carefully carried out, are almost always successful. Chronic constipation of years' duration in adults, the use of the barium sulfate meal and fecal masses formed by such substances as hygroscopic gums,²⁵⁴ colloidal aluminum hydroxide²⁵⁵ and the like, need but to be mentioned as possible causative factors in this condition. A careful report of a case of intestinal obstruction caused by colloidal aluminum hydroxide is of particular importance, as the patient to whom this preparation had been given died of intestinal obstruction. An obvious contributory factor was the concomitant administration of morphine over a period of days, in addition to the constant drip administration of the colloid. Practical therapeutic measures for treatment of fecal impaction are outlined by Benson and Bargen.

Because of the contribution of this anatomic finding to the production of intestinal disturbances, the description by Fine and Lawes²⁵⁶ of the muscle fibers of the anal submucosa, with special reference to the "pecten band," is of interest. Four biopsy specimens obtained from patients with annular thickening of the anal submucosa ("pecten band") showed that this thickening was due to dense bands of muscle fibers, which by comparison with other biopsy specimens were thought to be palpable manifestations of well developed submucosal muscle distinct from the internal sphincter. The term "*musculus submucosae ani*" is proposed for this submucosal muscle layer, which has apparently hitherto not been described and hypertrophy of which, due to various causes, leads to simple stenosis and symptoms of severe constipation.

The details of management necessary to successful surgical handling of the colon are outlined by various writers. The importance of maintaining a proper water and chemical balance is described accurately

253 Benson, K. W., and Bargen, J. A. Fecal Impaction, *Am J M Sc* **198** 541, 1939.

254 Wand, S. P. Fecal Impaction Due to a Hygroscopic Gum Laxative, *Am J Digest Dis* **7** 297, 1940.

255 Havens, W. P. Intestinal Obstruction Caused by Colloidal Aluminum Hydroxide, *J A M A* **113** 1564 (Oct 21) 1939.

256 Fine, J., and Lawes, C. H. W. On the Muscle Fibres of the Anal Submucosa with Special Reference to the Pecten Band, *Brit J Surg* **27** 678, 1940.

and in detail by Orr²⁵⁷ Although the facts presented have been recognized for some time, constant reiteration of the importance of such measures is proper Among disagreeable and sometimes dangerous symptoms following colonic operations are postoperative distention and urinary retention Again, the conclusions involved are not new, but the article by Marden and Williamson²⁵⁸ is of importance because these authors point out the therapeutic value of prostigmine methylsulfate in reducing the incidence of both complications The number of cases in which this drug was employed was sufficiently large to warrant the clinical impression that its use was attended by gratifying results The dangers of postoperative peritonitis incident to surgical treatment of the colon and rectum are so well known that use of sulfanilamide or its related compounds as a prophylactic measure was to have been expected Although the number of patients so treated is too small to warrant any absolute conclusions, Garlock²⁵⁹ indicates that use of this drug may be of value in reducing the dangers incident to this type of operation Postoperative infection by gas bacilli represents a serious complication of colonic procedures It is possible that sulfanilamide might be efficacious in dealing with such a serious complication, and the apparently successful therapeutic results obtained by Clute and Anglem²⁶⁰ in 2 cases of polyvalent gas bacillus infection of the abdominal wall complicating cecostomy done for obstructing colonic cancer warrant the inclusion of such a measure when indicated

Appendicitis—The occurrence of approximately half a million deaths from appendicitis in the United States during the past thirty years, or a loss of approximately 20,000 lives annually, and a note that appendicitis rates tenth as a cause of death in Canada are statistical statements warranting continued reference to a condition which should be easily recognized and successfully treated²⁶¹ That the high incidence of the disease is not limited to members of the white race is indicated

257 Orr, T G Water and Chemical Balance in Surgery of the Colon, *Am J Surg* **46** 70, 1939

258 Marden, P A, and Williamson, E G Use of Prostigmine Methylsulphate in Prevention of Postoperative Intestinal Atony and Urinary Bladder Retention, *Surg, Gynec & Obst* **69** 61, 1939

259 Garlock, J H, and Seley, G P Use of Sulfanilamide in Surgery of Colon and Rectum, *Surgery* **5** 787, 1939

260 Clute, H M, and Anglem, T J Gas Infection of Abdominal Wall, *New England J Med* **221** 647, 1939

261 Jackson, A S Half a Million Deaths from Appendicitis, *Illinois M J* **76** 355, 1939 Ochsner, A, and Murray, S Appendicitis, *Am J Surg* **46** 566, 1939 Munroe, A R, Hoare, E S, and Cristall, E Mortality of Appendicitis, *Canad M A J* **40** 463, 1939

by reports from the Philippines²⁶² and from the Netherland East Indies²⁶³. In the latter group, however, Fossen and Baeke record an interesting fact that they have apparently demonstrated in Batavia. A study of entries to the hospital due to acute appendicitis reveals that the incidence of this condition among the Europeans was definitely higher than among the Chinese or the native Netherland East Indians. However, the authors point out that histologic studies on the appendixes of the different racial stocks revealed that signs of inflammation occurred in a large percentage of appendixes incidentally removed in natives and Chinese. In fact, the morbidity of the condition among the latter was even higher than among the Europeans, but it seems that the clinical manifestations are much less frequent than among Europeans. It is also important to recall the fact, recited by Parsons,²⁶⁴ that statistics show that appendicitis in 50 per cent of all cases occurs within the first twenty years of life. In 25 per cent of this number it occurs between the ages of 1 and 5 years, and in 6 per cent, between the ages of 6 and 12 years. The mortality in children under 5 years of age averages from 15 to 25 per cent. Although statistical evidence on the subject is difficult to obtain, the article by Perry and Keeler²⁶⁵ suggests that some family pedigrees supply convincing evidence that peculiarities or anomalies of the appendix are inherited as simple dominant unit characters. The authors conclude from the literature and from their studies that there are a number of hereditary factors predisposing to appendicitis. In the family described the upper section of the pedigree includes an incidence of 65 per cent, whereas in the lower section more than five times as many cases are encountered. The pedigree presented by the authors is by far the most extensive yet placed on record.

The actual causation of appendicitis must involve several factors, but examination of the literature makes it apparent that in the majority of cases appendicitis is the result of a form of closed loop obstruction, most frequently due to the presence of an impacted fecalith, pinworms or some other agent of obstruction. An ingenious set of observations by Wangenstein and Dennis²⁶⁶ supports this thesis. The authors took occasion to note the behavior of a ligation of the appendix in 22

262 Estrada, J. J., and Meñez, S. C. 20,000 Cases of Appendicitis, *J. Philippine Islands M. A.* **19** 653, 1939.

263 Fossen, A., and Baeke, H. E. Frequency of Acute Appendicitis in Netherland East Indies, *Geneesk. tijdschr. v. Nederl.-Indie* **79** 2857, 1939.

264 Parsons, E. O. Appendicitis in Children, *J. Kansas M. Soc.* **41** 51, 1940.

265 Perry, T., Jr., and Keeler, C. E. Appendicitis in Single Family Pedigree, *Am. J. Surg.* **46** 259, 1939.

266 Wangenstein, O. H., and Dennis, C. Experimental Proof of Obstructive Origin of Appendicitis in Man, *Ann. Surg.* **110** 629, 1939.

patients, in whom it was possible to exteriorize the greater portion of the right half of the colon during operation for local cancer. Intraluminal pressures due to secretion of the thus ligated appendix were measured, and a pathologic picture identical to that of appendicitis was observed. In those instances in which there was no evidence of secretory pressure, luminal obstruction did not reproduce the picture of appendicitis. On the other hand, in those instances in which high secretory pressures were noted there was factual proof of such spontaneous appendicitis. The authors conclude that it appears likely that the chief inciting agency in bringing about appendicitis in man is obstruction of an appendix in which the mucosa (not atrophic) possesses normal secretory capacity.

The existence of appendicitis due to trauma is carefully discussed by Connell,²⁶⁷ who was able to obtain data in response to a questionnaire on the incidence of such a condition in only a few cases. Eighty-one surgeons operating in over 72,000 cases of acute appendicitis answered the questionnaire, but there was no uniformity of opinion. Answers to questions submitted to thirty hospitals reporting nearly 50,000 cases gave a history of trauma in only 11 cases, and the author is wisely skeptical of the theory that trauma, by forcing fecal contents into the appendix, is a cause of acute appendicitis. Pease²⁶⁸ also discusses the subject and asserts that traumatic appendicitis is a definite clinical entity that should be recognized not only by the physician but by the courts in questions of litigation and compensation. His study, however, is not nearly so complete and convincing as the preceding one.

The factors contributing to the mortality from acute appendicitis are well known and continue to be discussed in various articles. The duration of the disease before surgical intervention, the use of cathartics and the presence of diabetes certainly constitute the most important causes leading to an increased mortality. The well recognized increase in mortality from this condition among elderly persons is discussed carefully by Stalker.²⁶⁹ He points out the unfortunate fact that in spite of mild initial symptoms of cramplike pain and tenderness in the right lower abdominal quadrant combined with leukocytosis, which should properly lead to a correct diagnosis, progressive gangrene and rupture of the appendix during the succeeding forty-eight hours usually produce no acute symptoms, and the patient more frequently than not seeks no medical advice, at times remaining ambulatory until an abscess develops. For the more complicated conditions, associated with local

267 Connell, J. E. A. Trauma and Appendicitis, *Surgery* **7** 47, 1940.

268 Pease, G. N. Traumatic Appendicitis, *Journal-Lancet* **59** 539, 1939.

269 Stalker, L. K. Appendicitis Among Individuals More Than Sixty Years of Age, *Surg., Gynec. & Obst.* **71** 54, 1940.

or generalized peritonitis, the value of such procedures as duodenal decompression, transfusion, intelligent use of morphine and fluids, employment of sulfanilamide or related compounds and use of various serums or other measures to produce satisfactory local immune reactions is discussed in a large number of articles by different authors. These are chiefly of surgical interest, and a more complete treatment of this important subject may be found in a separate review.²⁷⁰

A recital of the diagnostic uncertainties of "chronic appendicitis" is important because of the surgical implications. Alvarez²⁷¹ is to be congratulated on his presentation of this controversial subject. His article properly condemns the poor surgical judgment frequently evinced in many cases in which a condition is so labeled and cites some figures and facts that are not given but are of interest. One of the causes for the mistaken diagnosis of appendicitis is the syndrome of abdominal pain secondary to mesenteric adenopathies. Again, this subject is not new but has been sanely discussed by Parini.²⁷²

Bacterial and Parasitic Diseases of the Intestine—The difficulties inherent in any bacteriologic study of the intestinal tract are well known, but results of intubation studies of the human small intestine obtained by Nichols and Glenn²⁷³ are of some interest. These authors studied the bacterial flora of the human throat, stomach and ileum, employing for the first time a Miller-Abbott tube to secure ileac specimens. Both aerobic and anaerobic cultures demonstrated a marked similarity in the organisms from the three areas, with variations in frequency rather than in type of bacteria noted. A further approach to the same subject is made by Porter and Rettger,²⁷⁴ who observed the influence of diet and the distribution of bacteria in the stomach, small intestine and cecum of the white rat. Contrary to much prevailing opinion, the stomach and small intestine of the albino rat under most dietary conditions contained appreciable numbers of viable bacteria.

270 Jones, C. M. Report on Medical Progress. Gastroenterology, New England J Med **222** 634, 1940.

271 Alvarez, W. C. When Should One Operate for Chronic Appendicitis? Study of Three Hundred and Eighty-Five Cases, J A M A **114** 1301 (April 6) 1940.

272 Parini, A. Abdominal Syndromes from Adenopathies of Mesentery, Arch ital di chir **56** 314, 1939.

273 Nichols, A. C., and Glenn, P. M. Intubation Studies of the Human Small Intestine. XVI. The Bacterial Flora of the Ileum Compared with That of the Throat and Stomach in Normal Subjects, J Lab & Clin Med **25** 388, 1940.

274 Porter, J. R., and Rettger, L. F. Influence of Diet on the Distribution of Bacteria in the Stomach, Small Intestine and Cecum of White Rats, J Infect Dis **66** 104, 1940.

The so-called normal bacterial flora can be altered throughout the digestive tract by certain foods or by starvation, but it is fairly stable irrespective of the diet. Once the flora has been changed, it can be transformed back to normal by administration of appropriate diets. In a few instances, there appeared to be a relation between the hydrogen ion concentration of the contents of the lower part of the ileum and the cecum, the bacteriologic picture and the diets employed.

Carbohydrate intolerance in cases of intestinal fermentation or fermentative diarrhea is undoubtedly associated with abnormal intestinal flora. Serious consideration is given to this condition by Holmgren²⁷⁵ in an article which is of interest because he reviews many of the bacteriologic studies that have been made and indicates the high incidence of hypochlorhydria or achlorhydria. The symptoms are thoroughly described, but one cannot entirely agree with the author's enthusiasm in attempting to dignify the syndrome by considering it true enterocolitis. The value of a low carbohydrate diet for this condition and possibly for true colitis is discussed by Voegtlin²⁷⁶. Both he and Oppenheimer²⁷⁷ indicate the frequent increase in flatulence due to fermentation or colonic irritability when cathartics or other "cleansing" agents are utilized, and the latter gives a rather admirable discussion on the entire subject of "gas in the bowels" and its clinical significance in conditions not associated with increased fermentation.

Specific infection of the intestinal tract by a tubercle bacillus is noted with decreasing frequency by the average practitioner of medicine, as patients suffering from such conditions tend more and more to become segregated in institutions for the treatment of tuberculosis. The accurate diagnosis of intestinal tuberculosis, however, is still extremely important, although no exact specific procedures are as yet available. Careful roentgen study, sigmoidoscopy and stool examinations, which may exclude other conditions and present suggestive evidence of tuberculous involvement, must be carried out in numerous cases of diarrhea before a final diagnosis is possible. Roentgen diagnostic criteria have already become fairly widely recognized since the extensive studies of Brown and others. Valuable clinical and pathologic studies of this condition are those by Hardt and his collaborators,²⁷⁸ Bellinger,²⁷⁹

275 Holmgren, I. Fermentative Dyspepsia and Fermentative Enterocolitis, *Acta med Scandinav* **99** 476, 1939.

276 Voegtlin, W. L. Low Carbohydrate Diet in Functional Disorders of the Large Bowel, *Northwest Med* **38** 252, 1939.

277 Oppenheimer, A. Gas in the Bowels. Observations and Experiments in Man, *Surg, Gynec & Obst* **70** 105, 1940.

278 Hardt, L. L., Weissman, M., Cook, C. E., and Martin, C. L. Tuberculous Enterocolitis. Diagnostic Data, *Illinois M J* **76** 229, 1939.

279 Bellinger, G. C. Diagnosis and Treatment of Intestinal Tuberculosis, *Northwest Med* **38** 344, 1939.

Freilich and his co-authors²⁸⁰ and Cullen²⁸¹ That tuberculous enterocolitis can exist in the absence of active pulmonary involvement is still not sufficiently well recognized, and the report of Bockus, Tumen and Kornblum²⁸² adds an excellent discussion of this particular clinical procedure Because of the high incidence of viable and virulent tubercle bacilli in the lower part of the sigmoid flexure of the colon and the rectum in cases of pulmonary tuberculosis, with the consequent probability of tissue contamination, Martin, Lansford and Sweany²⁸³ contribute the important observation that stool cultures and animal inoculation are of little value in establishing the tubercle bacillus as a cause of anal fistula or abscess, in contrast to the real value of histopathologic examination of the tissues

Continued observations on the value of intramuscular injections of calcium gluconate in the treatment of intestinal tuberculosis are found in an article by Pisani,²⁸⁴ although the author recognizes that extensive postmortem observations are still needed before definite conclusions as to the value of this particular form of treatment can be drawn He also admits the difficulty of treatment of intestinal tuberculosis unless the pulmonary lesions that are almost invariably present are under complete control

The differential diagnosis of the diarrheas involves consideration of so many etiologic factors that a complete survey of the literature on this subject is not permissible in this review A good summary of the situation is that by Manson,²⁸⁵ who in a rather textbook-like fashion presents a complete summary of all the possible causes of such a symptom The article includes a discussion not only of bacterial and parasitic agents but of such constitutional conditions as pernicious anemia, endocrine disturbances and avitaminosis

Numerous reports on infantile diarrheas are encountered Snyder²⁸⁶ made an interesting investigation of fecal flora in 22 normal infants under

280 Freilich, E B , Coe, G C , and Wien, N A Gastrointestinal Tuberculosis Correlation of Clinical Diagnoses and Autopsy Findings in Eighty Cases, with Review of Literature, *Rev Gastroenterol* **6** 483, 1939

281 Cullen, J H Intestinal Tuberculosis Clinical Pathological Study, *Quart Bull, Sea View Hosp* **5** 143, 1940

282 Bockus, H L , Tumen, H , and Kornblum, K Diffuse Primary Tuberculous Enterocolitis, *Ann Int Med* **13** 1461, 1940

283 Martin, C L , Lansford, W I , and Sweany, H C Etiology of Tuberculous Anal Abscess and Fistula, *Am J Digest Dis* **7** 36, 1940

284 Pisani, V V Intestinal Tuberculosis and Calcium Gluconate, *Am Rev Tuberc* **40**:571, 1939

285 Manson, T J Differential Diagnosis of the Diarrheas, *J Tennessee M A* **32** 276, 1939

286 Snyder, M L Normal Fecal Flora of Infants Between Two Weeks and One Year of Age I Serial Studies, *J Infect Dis* **66** 1, 1940

1 year of age Carey²⁸⁷ provides a good clinical discussion of the gastrointestinal symptoms associated with infections of the respiratory tract in children and several good descriptions²⁸⁸ of epidemics of infantile diarrhea in different parts of the world are available. An imposing number of carefully authenticated, bacteriologically proved accounts of epidemics in children and adults due to Shiga, Flexner, Sonne, "Newcastle" and unrelated dysentery bacilli, the various members of the Salmonella group, Gartner bacillus (*Bacterium enteritidis*), staphylococcus and nonhemolytic short chain streptococcus are to be found²⁸⁹. Their appearance in the current literature not only is indicative of the multiple factors present as possible causative agents in epidemic diarrheas but attests the increasing appreciation of their importance. This is particularly true when one notes the widespread geographic distribution of these various reports.

287 Carey, J. F. Gastrointestinal Symptoms of Respiratory Infections in Children, *Illinois M J* **76** 325, 1939.

288 Castello, J. P., and Lind, H. E. Epidemic of Nursery Diarrhea, *South M J* **32** 620, 1939. Barrera, B. The Pathology and Bacteriology of Ileocolitis in Children, *J Philippine Islands M A* **19** 345, 1939. Smellie, J. M. Infantile Diarrhea, *Lancet* **1** 1026, 1939.

289 Cooper, M. L., Furcolow, M. L., Mitchell, A. G., and Cullen, G. E. Relation of Dysentery to Acute Diarrhea of Infants and Children, *J Pediatr* **15** 172, 1939. Hardy, A. V., Watt, J., Kolodny, M. H., and De Capito, T. Studies of the Acute Diarrheal Diseases. III Infections Due to the "Newcastle Dysentery Bacillus," *Am J Pub Health* **30** 53, 1940. Woolpert, O. C., Marsh, H. F., and Yaw, O. K. Bacillary Dysentery Resulting from an Accidental Laboratory Infection, *J A M A* **113** 753 (Aug 23) 1939. Tulloch, W. J. Observations Concerning Bacillary Food Infection in Dundee During 1923-1938, *J Hyg* **39** 324, 1939. Beck, A., and Buckle, D. F. Bacteriological Findings in an Epidemic of Sonn  Dysentery, *ibid* **39** 311, 1939. Block, N. B., and Ferguson, W. An Outbreak of Shiga Dysentery in Michigan in 1938, *Am J Pub Health* **30** 43, 1940. Godfrey, E. J., and Pond, M. A. A Hospital Epidemic of Flexner Dysentery Caused by Contaminated Ice, *J A M A* **114** 115 (March 30) 1940. Massey, L. D., and Louckes, H. A Study of Bacillary Dysentery, *J Arkansas M Soc* **36** 180, 1940. Guthrie, K. J., and Montgomery, G. L. Infections with *Bacterium Enteritidis* in Infancy with Triad of Enteritis, Cholecystitis and Meningitis, *J Path & Bact* **49** 393, 1939. Brown, E. G., Combs, G. R., and Wright, E. Food-Borne Infection with *Salmonella Aertrycke*, *J A M A* **114** 642 (Feb 24) 1940. Birge, E. A. Similarity of Chronic Infections with *Salmonella Typhimurium* and Tuberculosis in Guinea Pigs, *Am J Pub Health* **29** 1125, 1939. Schiff, F., and Strauss, L. Occurrence of Several Unusual Types of *Salmonella* in Human Infections, *J Infect Dis* **65** 160, 1939. Abele, C. A., and Damon, S. R. Outbreak of Gastro-Enteritis Caused by Milk-Borne Staphylococci Producing an Enterotoxin, *J M A Alabama* **9** 1, 1939. Slocum, G. G., and Linden, B. A Food Poisoning Due to Staphylococcus, with Special Reference to Staphylococcus Agglutination by Normal Horse Serum, *Am J Pub Health* **29** 1344, 1939. Minor, L. W. An Outbreak of Gastro-Enteritis in Middletown in 1938, *J Connecticut M Soc* **3** 615, 1939.

As was to be expected, nearly all of these epidemics appear to have been spread by food handlers, and they illustrate the existing need for further education of the public and of physicians in public health measures directed toward prevention of these communicable diseases. They also indicate clearly the obligation, as well as the opportunity, for the practicing physician to attempt through hospital or public health laboratories a search for the causative agents of many of the more important forms of infectious diarrhea.

The importance of vitamin deficiency as a factor conducive to the development of bacillary dysentery is suggested by the studies of Janota and Dack.²⁹⁰ These authors demonstrated that monkeys which were known to be carriers of Flexner organisms generally showed clinical manifestations of bacillary dysentery when placed on a diet deficient in vitamin "M."

Animal experimentation on the value of protective vaccines against various organisms of the dysentery bacillus group and immunologic studies on human subjects are reported by Prigge.²⁹¹ Encouraging results in animals were definitely obtained, and serologic tests on human subjects disclosed the appearance of specific protective substances in the blood. A final estimate of the efficacy of these endotoxin-toxin-anti-serum vaccines (ETA) on the basis of clinical experience is still to be made, but it is already known that polyvalent Flexner bacillus vaccine can be used with some success as a prophylactic measure. Prigge points out, however, that if vaccine treatment against dysentery is to be put into practice, the polyvalent mixed vaccines must be employed. These contain, in addition to the antigens of the Shiga-Kruse group, those of the more important "toxin deficient" dysentery bacilli and of the Flexner and Kruse-Sonne groups.

Two articles²⁹² on the value of transfused blood taken from artificially immunized donors in the treatment of chronic bacillary dysentery are also of some interest, although the number of patients treated was insufficient for any adequate conclusions as to the efficacy of such a maneuver.

It was inevitable that the effects of sulfanilamide on bacillary dysentery should be given a clinical trial. Jones and Abse,²⁹³ after

290 Janota, M., and Dack, G. M. Bacillary Dysentery Developing in Monkeys on "Vitamin M" Deficient Diet, *J. Infect. Dis.* **65** 219, 1939.

291 Prigge, R. Active Protective Vaccination Against Bacillary Dysentery, *Klin. Wchnschr.* **19** 337, 1940.

292 Felson, J. C. Clinical Notes on the Use of Immunized Donors in Chronic Bacillary Dysentery, *Am. J. Digest. Dis.* **7** 81, 1940. Turell, R. Transfusion of Blood from Artificially Immunized Donor in the Treatment of Chronic Bacillary Dysentery, *J. Lab. & Clin. Med.* **25** 706, 1940.

293 Jones, E., and Abse, D. W. Sulfanilamide Therapy in Bacillary Dysentery, *J. Ment. Sc.* **85** 1259, 1939.

laboratory experiments, gave sulfanilamide to 21 patients suffering from bacillary dysentery (Flexner W). Uniformly favorable results were noted, and it is to be hoped that further observations, including studies on the effect of the drug on dysentery carriers, will be made. The use of pectin, pectin agar and metal pectinates in the treatment of infectious diarrheas continues to attract attention, and articles²⁹⁴ from the laboratories and clinics continue to appear, testifying to the therapeutic value of these preparations in cases of bacillary dysentery and other forms of bacterial invasion of the intestinal tract. Perusal of the literature would seem to warrant the conclusion that pectin-containing substances, particularly when combined with metallic ions, such as nickel, possess definite bacteriostatic and bactericidal properties, especially in the more acute infectious diarrheas. Whether these preparations offer more than palliative relief of the more serious or chronic forms of diarrhea due to bacterial invasion of the intestine is open to real question, and it must also be remembered that from many of the acute forms of infectious diarrhea the patients recover rapidly with almost any simple form of therapy. Further carefully controlled clinical studies on the use of such preparations are needed before any final conclusion can be reached as to their efficacy.

While considering infections of the intestinal tract, it is important to call attention to a further observation by Kramer and his associates,²⁹⁵ who continue their search to recover the virus of poliomyelitis from the intestinal contents. During an epidemic of poliomyelitis in a children's home, the authors isolated the virus from the stools of 3 of 12 healthy children who had been in contact with patients suffering from the disease and from 2 of 3 other children who had noticeable fever but no clinically diagnostic paralysis. Thus, including the 5 with clinical infections, 10 of the 20 children who were in contact harbored the poliomyelitis

294 Manville, J. A., and Sullivan, N. P. Relationship of the Diet to the Self-Regulatory Defense Mechanism. III. Organic Acids and Pectin, *Am J Digest Dis* **7** 111, 1940. The Bactericidal Action of Metallic Ions in Broth Containing Dehydrated Apple, *ibid* **7** 106, 1940. Cruz, F. Z. Local Observation on the Use of Fresh Apple in Gastro-Enteritis, *J Philippine Islands M A* **19** 611, 1939. Kutscher, G. W., Jr. The Role of Pectin in Diarrhea, *North Carolina M J* **1** 107, 1940. Kutscher, G. W., Jr., and Blumberg, A. The Use of Pectin Agar Mixtures in Diarrheas, *Am J Digest Dis* **6** 717, 1939. Winters, M., Tompkins, C. A., and Crook, G. W. Pectin Agar Diets in Treatment of Bacillary Dysentery of Infants and Children, *J Pediat* **14** 788, 1939. Myers, P. B., and Rouse, A. H. Pectinates with Special Reference to Nickel Pectinate and Their Therapeutic Value, *Am J Digest Dis* **7** 39, 1940.

295 Kramer, S. D., Gilliam, A. G., and Molner, J. G. Recovery of Virus of Poliomyelitis from Stools of Healthy Contacts in Institutional Outbreak, *Pub Health Rep* **54** 1914, 1939.

virus at some time, and the virus was also found in the stool of the day nurse in charge. From the public health point of view, the importance of these findings is obvious. Also of public health interest is the note by Tucker and Swanson²⁹⁶ of a small outbreak of botulism due to botulinus toxin subsequently demonstrated to be present in home-canned vegetables.

A constantly growing recognition of the important role of gastrointestinal parasites in man as the cause of displeasing or dangerous symptoms is evident in the gastroenterologic literature of recent years. Detailed reports²⁹⁷ on human intestinal parasites from such widely separated areas as Alabama, the northeastern seaboard states, Indiana, Colorado and Saskatchewan indicate the importance of and interest in such conditions. Particular interest centers on the infestation of the digestive tract with *Endamoeba histolytica*, but to those physicians not entirely familiar with methods of search for other parasites, such as *Ascaris*, *Taenia nana*, *Trichiuris trichiura* and others, careful perusal of these articles will be of benefit.

The more serious aspects of amebic infestation are well recognized. The clinical significance of the carrier still, however, is an important consideration, and a study by Howard²⁹⁸ on 22 carriers of *E. histolytica* is of some interest as regards the effect of therapy on minor symptoms commonly attributable to this condition. Only one fourth of his patients were freed from abdominal symptoms by specific antiamebic treatment. Such a result indicates the wisdom of searching for amebiasis in patients with vague gastrointestinal complaints, but too striking clinical improvement should not be expected from the amebicidal treatment of carriers. This conclusion is not in keeping with those expressed by many writers who are more enthusiastic than critical concerning the therapeutic results of specific medication. A somewhat similar clinical study by Saperio²⁹⁹ of cases of nondysenteric intestinal amebiasis indicates the incidence of minor digestive symptoms in amebic carriers, as contrasted with the rela-

296 Tucker, C. B., and Swanson, H. Outbreak of Botulism in Tennessee Due to Type B *Clostridium Botulinum*, *Pub Health Rep* **54** 1556, 1939.

297 Smith, W. H. Y., Gill, D. G., and McAlpine, J. G. Intestinal Parasite Survey in Alabama, *South M J* **32** 1094, 1939. Connell, F. H., and French, H. T. The Incidence and Results of Treatment of Subclinical Amebiasis, *J A M A* **113** 649 (Aug 19) 1939. Kmeczka, J. M. The Incidence of Human Intestinal Parasite Infections Among Patients in a State Institution of Indiana, *Am J Trop Med* **19** 515, 1939. Chisholm, A. J. Amebiasis, *Rocky Mountain M J* **36** 870, 1939. Miller, M. J. Intestinal Protozoa of Man in Saskatchewan, *Canad M A J* **41** 120, 1939.

298 Howard, J. T. The Clinical Significance of the Carrier State in Amebiasis, *Am J Digest Dis* **6** 506, 1939.

299 Saperio, J. J. Clinical Studies in Nondysenteric Intestinal Amebiasis, *Am J Trop Med* **19** 497, 1939.

tive freedom from complaints of patients harboring many other parasites. Again, hospitalization and antiamebic treatment were beneficial only in a rather carefully chosen group of patients harboring this infestation without dysenteric symptoms. An unusual opportunity for a study of the food handler as a transmitter of amebiasis is that recorded by Schoenleber³⁰⁰. He reports observations made in the island of Aruba, to which were transported 1,500 Americans recruited from localities in the United States where the average amebic infestation rate is not more than 10 per cent. These persons lived for years in the island without prophylactic measures against dissemination of amebic infestation by carriers. The group lived under conditions which precluded the possibility of acquiring it from water, flies, sewage or soil contamination of food. Examinations of the stool after some period of residence showed an annual infestation rate of 25 per cent and an amebic colitis rate of 36 per thousand. Examinations of the stools of food handlers showed that one third were carriers. As a result of active measures for control of dissemination of the infestation only by food handlers, the infection rate was reduced 50 per cent after one year and 92 per cent after three years of such activities, a valuable and conclusive experience in the efficacy of specific public health measures.

For a rather complete review of all the accepted methods of antiamebic therapy, the reader is referred to recent articles by Shattuck³⁰¹ and by Mateer and others,³⁰² who discuss in detail the utilization of emetine, carbarsone, chinofon and vioform, with their various indications and contraindications. A report from Batavia by van Wesel³⁰³ recites his experiences with the use of arsphenamine preparations in the treatment of amebic dysentery and amebic hepatitis refractory to other drugs. The results reported are not entirely conclusive but without question warrant serious consideration of such a procedure for otherwise intractable conditions. Amebic granuloma is most frequently located in the cecum and in the flexures of the colon. It occasionally occurs in the rectum, however, and may readily be mistaken for a malignant growth, as the associated symptoms and proctoscopic appearance are not dissimilar to those of carcinoma, indeed the two conditions may be combined in a single lesion. Biopsy of such lesions is of the utmost impor-

300 Schoenleber, A. W. The Food Handler as a Transmitter of Amebiasis, *Am J Trop Med* **20** 99, 1940.

301 Shattuck, G. C. Treatment of Amebiasis, *M Clin North America* **23** 1269, 1939.

302 Mateer, J. G., Baltz, J. I., Marion, D. E., and Hollands, R. A. The Treatment of Amebiasis by a Combined Method. Statistical End Results, *Am J Digest Dis* **7** 154, 1940.

303 van Wesel, R. Treatment of Amebic Dysentery and Amebic Hepatitis with Arsphenamine, *Geneesk tijdschr v Nederl-Indie* **79** 825, 1939.

tance, and 3 such cases are reported by Hummel³⁰⁴ and by Donald and Brown³⁰⁵. The identity of the lesion was established by microscopic examination of scrapings obtained through a sigmoidoscope, and specific therapy 5,7-diiodo-8-hydroxyquinoline (diiodoquin) produced entirely satisfactory results. The surgical aspect of amebiasis is completely summarized by Ochsner and DeBakey,³⁰⁶ who present an excellent review of the subject in all its details. To those unfamiliar with these more serious aspects of infection by this particular parasite, the article is worthy of very careful reading. On the basis of Craig's estimate that between 6,000,000 and 12,000,000 persons in the United States are infected with *E. histolytica* and the known fact that hepatic complications occur in approximately 4 to 5 per cent of persons with amebic dysentery, it can be readily seen that a knowledge of its significance, diagnosis and treatment is of real clinical importance.

The important diagnostic aid to be obtained by careful roentgen examination in cases of colonic disease of obscure origin is still not well recognized by many roentgenologists and internists. Various abnormalities of the colon may be recognized in the subchronic and chronic forms of amebic dysentery, the most characteristic finding being segmental distribution of narrowed or atonic bowel. These findings are carefully reviewed in an article by Meves,³⁰⁷ of Leipzig, Germany, who examined a large group of persons who had previously contracted amebic dysentery and who had persistent symptoms in spite of previous therapy.

Few reports of disease due to *Balantidium coli* in this country have appeared prior to one by Young,³⁰⁸ who adds a record of 9 cases from South Carolina and Tennessee to the 32 cases already to be found in the literature. Swine are generally thought to be the source of most such infections in man, but epidemiologic studies indicate that in the cases under discussion the infections were contracted from human sources. The infected patients had chronic diarrhea and occasional acute dysenteric attacks, but it is not clear that the symptoms were entirely due to infestation by *Balantidia*, as 3 other parasites were also found as a result of frequent examinations of the stool. Carbarsone therapy resulted in the disappearance of *Balantidia* from the stools in 2 patients, but oil of chenopodium given orally appeared to be ineffective.

304 Hummel, H. G. Amebic Granuloma of the Rectum and Balantidiasis in the Same Patient, *Am J Digest Dis* **7** 178, 1940.

305 Donald, C. J., Jr., and Brown, P. W. Amebic Granuloma Simulating Carcinoma of the Rectum, *Proc Staff Meet, Mayo Clin* **15** 331, 1940.

306 Ochsner, A., and DeBakey, M. *Surgery of Amebiasis*, New Orleans M & S J **91** 670, 1939.

307 Meves, F. Roentgenographic Observations in Chronic Amebic Dysentery, *Fortschr a d Geb d Rontgenstrahlen* **60** 175, 1939.

308 Young, M. D. Balantidiasis, *J A M A* **113** 580 (Aug 12) 1939.

A detailed analysis of 81 uncomplicated clinical cases of Trichocephalus (whipworm) infection is presented by Swartzwelder³⁰⁹ More than two thirds of the patients were in the age group between 6 and 15 years. White patients predominated over Negroes in the ratio of 5 to 1, and there were twice as many females as males. The fact that a diagnosis of chronic appendicitis was made in an appreciable number of instances indicates the importance of infestation with this parasite as a cause of vague abdominal symptoms.

The symptomatology of oxyuriasis is thoroughly discussed by Brady and Wright³¹⁰ after careful study of 200 cases. The opinion is expressed that symptoms may be caused by mechanical stimulation and irritation, by allergic reactions or by transportation of the organisms to places where they may become pathogenic. Conscious sensations and enuresis were not common, but evidence is presented that pinworm vaginitis may be much more frequent than it has usually been considered. No abnormal sensations were noted in the majority of cases after the pinworm had migrated onto the skin from the rectal and anal mucosa. In only 1 case of the 200 had appendectomy been performed, and no proof was found that any true relation existed between the occurrence of oxyuriasis and abdominal pain. Moderate eosinophilia was found in over two thirds of the children. Successful treatment was accompanied with an improvement in appetite, weight and color. The same authors³¹¹ present a convincing report on the efficacy of gentian violet in the treatment of pinworm infestation. A total of 224 patients were treated by oral administration of this drug, with exceptionally satisfactory results. A detailed description of the more efficacious methods of treatment, with the contraindications for the use of gentian violet, is given, and the authors seem to be entirely justified in their conclusion that "gentian violet is cheaper and superior to all other methods of treatment." The article offers a valuable contribution to the therapy of this common and frequently intractable and annoying condition. A further contribution is that of Sawitz³¹² and her associates, who demonstrate in rather conclusive fashion the superiority of Hall's cellophane-tipped swab method in the

309 Swartzwelder, J. C. Clinical Trichocephalus Trichurias Infection, *Am J Trop Med* **19** 473, 1939.

310 Brady, F. J., and Wright, W. H. Studies on Oxyuriasis. The Symptomatology of Oxyuriasis as Based on Physical Examinations and Case Histories on Two Hundred Patients, *Am J M Sc* **198** 367, 1939.

311 Wright, W. H., and Brady, F. J. Efficacy of Gentian Violet in the Treatment of Pinworm Infestation, *J A M A* **114** 861 (March 9) 1940.

312 Sawitz, W., Odom, V. O., and Lincicome, D. R. Diagnosis of Oxyuriasis. Comparative Efficiency of the N. I. H. Swab Examinations and Stool Examination by Brine and Zinc Sulfate Floatation for Enterobius Vermicularis, *Pub Health Rep* **54** 1148, 1939.

diagnosis of oxyuriasis, which proved to be infinitely superior to the examination of stools by the bime or the zinc sulfate method. Initial swab examinations revealed infection in three fourths of 136 children examined, but at least seven swab examinations were necessary before the absence of pinworm infestation was assured, as subsequent tests by this method revealed an incidence of 96.3 per cent in the same group.

The role of *Giardia* in the production of gastrointestinal symptoms is still controversial. That the duodenum is frequently the seat of giardial infestation in man is well known, particularly since investigation of duodenal contents has become a routine procedure. An increasing number of reports seem to contain suggestive evidence that human giardiasis is associated with real but rather indefinite disturbances of the digestive tract, which may be relieved by appropriate therapy. The efficacy of atabrine as the most potent parasiticide available for the treatment of giardial infestation is becoming more apparent. A recent report by Morrison and Swalm³¹³ indicates the value of such therapy as originally outlined by Valerio, and the authors appear to be entirely warranted in their conclusion that "Despite the absence of control studies, atabrine is definitely helpful clinically in some of the cases." A further article, by Veghelyi,³¹⁴ is also of interest in this regard. He has made studies on absorption of fat and excretion of urinary pigment in a group of children infested with *Giardia* but without evidence of any other disease. In these children absorption of fat was found to be greatly defective, and only a small part of the normal amount of urinary pigment was excreted. Such findings were attributed to the mechanical effect of the parasites on intestinal function. Veghelyi feels that the symptoms commonly attributed to giardiasis in children—anemia and retardation of development—can be adequately explained on the basis of deficient fat absorption. After appropriate therapy, with expulsion of parasites, all symptoms disappeared, the fat absorption and pigment content of the urine became normal, anemia improved and growth commenced.

The high incidence of *Trichinella* infestation in the United States is well recognized. Examination by Nolan and Bozicevick in 1938 of 1,000 cadavers from different hospitals in Washington and other eastern cities revealed an incidence of 17.4 per cent, and other surveys provide figures ranging from 3.5 to 27 per cent of the local population. It is characteristic, however, of all these findings that very light, nonclinical conditions predominate. A report from North Carolina by Harrell and Johnston,³¹⁵ based on examinations of necropsy material revealed an incidence of

313 Morrison, L. M., and Swalm, W. A. A New Effective Parasiticide in Giardiasis, *Am J Digest Dis* 6:325, 1939.

314 Veghelyi, P. V. Giardiasis, *Am J Dis Child* 59:793 (April) 1940.

315 Harrell, G. T., and Johnston, C. Incidence of Trichinosis in the Middle South, *South M J* 32:1091, 1939.

trichinosis in the middle part of the South that appears to be much less than that reported in other sections of the country. The conclusions of these authors are of importance if they are correct. They attribute the lower incidence to the fact that trichinosis, which is a hog-borne disease, is probably caused by meat from garbage-fed hogs. Most southern hogs are grain fed, and the incidence of trichinosis in hogs and in human beings in this particular section of the country appears to be lower than elsewhere. Another fact that may contribute to the paucity of clinical cases of trichinosis as compared with the admittedly large number of infestations in human beings is suggested by the experimental studies of Roth,³¹⁶ who was able to establish successful immunity in guinea pigs to reinfections with *Trichinella spiralis*. This immunity to reinfection appeared to be due to a defense mechanism, which apparently inhibits the maturing and propagation of larvae, but the problem is still unsolved, although it is possible that such immunization may occur in man and may in part account for the infrequency of diagnosable disease.

One point of practical importance in relation to parasitic disease is its frequent association with deficiency disease. Such an association is rather obvious, but the need for general dietary supervision in addition to specific antiparasitic therapy is indicated, for example, in the report by McKenzie,³¹⁷ who discusses vitamin B₁ deficiency associated with hookworm anemia. He draws particular attention to the rapid disappearance of edema so frequently noted in cases of hookworm infestation following the addition of vitamin B₁ to the usually accepted forms of treatment.

Regional Enteritis—Regional enteritis as a disease entity is now generally recognized, and its diagnosis is made with relative frequency, but therapeutic measures still leave much to be desired. Obstructive symptoms due to stenosis or to fistula formation obviously require surgical intervention. It is still not clear whether the ulcerative stage of the disease, characterized by varying degrees of abdominal cramps, diarrhea, the occurrence of anemia and loss of weight is best treated by the surgeon. That a reasonable doubt exists as to the efficacy of surgical intervention under such conditions is expressed to an increasing degree by various authors. Holloway³¹⁸ and Rhoads,³¹⁹ for example, present a general discussion of the features of this interesting disease, and both recommend conservative treatment in certain of its phases. As Holloway

316 Roth, H. Experimental Studies on the Course of Trichina Infection of Guinea Pigs. III. Immunity of Guinea Pigs to Reinfection with *Trichinella Spiralis*, *Am J Hyg (Sect D)* **30** 35, 1935.

317 McKenzie, A. Deficiency of Vitamin B₁ in Hookworm Anemia, *Lancet* **1** 1143, 1939.

318 Holloway, J. W. Regional Ileitis, *Ohio State M J* **35** 1059, 1939.

319 Rhoads, J. E. The Management of Regional Ileitis and Certain Other Ulcerative Lesions of the Intestines, *Pennsylvania M J* **42** 1050, 1939.

expresses it "There is some difference of opinion, but there is little support for immediate radical resection," as the course to follow when one encounters acute regional enteritis at operation. As Rhoads points out and as is evident from other scattered observations, regional enteritis may occur in an early form with little fibrosis. When gross evidence of fibrosis is not evident, expectant treatment is indicated, "as resolution is frequent." While commenting on the indications and the results of surgical intervention, Rhoads points out an additional aid in the management of obstructive symptoms, namely, decompression by means of the Miller-Abbott tube.

The satisfactory results obtained in a group of cases by Landa and Stritzko³²⁰ following the use of such nonspecific measures as fever therapy with injections of foreign proteins lends weight to the suggestion that medical management of many of these conditions not only is justifiable but may be consistent with excellent results. However, further prolonged clinical observations of this disease are needed before adequate and convincing knowledge is obtained as to the precise therapeutic measures to be employed.

The close association between profound nutritional disturbances and regional enteritis is readily understood. Hypoproteinemia and avitaminosis are fairly well recognized complications, and that such a deficiency may invalidate what might otherwise prove to be successful surgical intervention is pointed out by Casten³²¹. He reports 1 such case, in which complete and persistent absence of healing of the abdominal incision was noted during the entire postoperative course, in spite of the fact that no semblance of an infection was present. It seems possible that this failure of wound healing may have been due to vitamin C deficiency. Severe anemia is commonly observed in association with regional enteritis. Plum and Warburg³²² review the literature on a large group of cases and find mention of hyperchromic anemia only once. The authors record observations on 3 additional cases in which the picture was that of severe megalocytic anemia and in 2 of which the patients responded completely to liver therapy. It is of interest to note that in 1 case the blood picture has been completely normal for more than one year without any further treatment with liver. Two patients also showed clinical evidence of pellagra and peripheral neuritis, which responded to vitamin B therapy. The authors make the entirely proper

320 Landa, E, and Stritzko, G. Fever Therapy in Chronic Enterocolitis, *Wien Arch f inn Med* **33** 145, 1939.

321 Casten, D. Nutritional Disturbances in Regional Enteritis, *Surgery* **6** 708, 1939.

322 Plum, P, and Warburg, E. Hematological Changes, Especially Megalocytic Anemia in Regional Ileitis, *Acta med Scandinav* **102** 449, 1939.

suggestion that some of the regional changes in the ileum itself may represent secondary changes in a vicious cycle

Ulcerative Colitis—Continued observations on the etiology of ulcerative colitis fail to reveal any definite specific causative organism and confirm the impressions of Paulson and many others, who consider the disease as a syndrome possibly due to a variable but not yet positively demonstrable cause. Bacteriologic studies by Reed,³²³ Dack and his associates³²⁴ and Mintzer³²⁵ serve to illustrate the variety of bacterial invaders considered as possible causes of this serious disease. Additional evidence that indirectly confirms the previously reported work of Lum on the effect of vasospasm in the causation of ulceration of the intestinal mucosa is presented in the experimental results reported by Penner and Bernheim³²⁶. Conditions of shock were reproduced by continued intraperitoneal injections of epinephrine, with the production of necrotic and ulcerated lesions at different levels in the gastrointestinal tract. That such vasospasm may produce ulceration and at the same time be due to the influence of neurogenic factors is of importance in any consideration of the possible etiologic relation between profound psychogenic disturbances and ulcerative colitis.

A statistical study by Jackman, Barger and Helmholz³²⁷ on the incidence of ulcerative colitis in children is of value because it indicates the more serious nature of the condition in the earlier decades of life.

The clinical manifestations of this disease have been so frequently described that there is no necessity for reviewing many of the articles that have appeared, which are purely descriptive of the ordinary manifestations to be encountered. Allusion to a single article by Smith and Jackman,³²⁸ however, is warranted, as it calls particular attention to the anorectal complications of the disease. These are frequently encountered and are not only distressing but extremely difficult to treat satisfactorily. Anal abscess or fistula constitutes one of the most common complications.

323 Reed, A. C. Chronic Ulcerative Colitis, *California & West Med* **50** 402, 1939, **51** 32, 1939

324 Dack, G. M., Kirsner, J. B., Dragstedt, L. R., and Johnson, R. Agglutinins for *Bacterium Necrophorum* in Serum of Patients with Chronic Ulcerative Colitis, *J. Infect. Dis.* **65** 200, 1939

325 Mintzer, I. J. Pyoderma Gangraenosum, Onychogryphosis and Onycholysis with Ulcerative Colitis, *Arch. Dermat. & Syph.* **40** 541 (Oct.) 1939

326 Penner, A., and Bernheim, A. Experimental Production of Digestive Tract Ulceration, *J. Exper. Med.* **70** 453, 1939

327 Jackman, R. J., Barger, J. A., and Helmholz, H. F. Life Histories of Ninety-Five Children with Chronic Ulcerative Colitis. Statistical Study Based on Comparison with a Whole Group of Eight Hundred and Seventy-One Patients, *Am. J. Dis. Child.* **59** 459 (March) 1940

328 Smith, N. D., and Jackman, R. J. Anorectal Complications of Chronic Ulcerative Colitis, with Several Illustrative Cases, *Surgery* **7** 69, 1940

of chronic ulcerative colitis, and in the series of patients reported on by these authors it ranked third, polyposis and stricture occurring more frequently, in the order named. The authors also made one recommendation of great importance, which is so frequently overlooked that it will bear repetition. They stress the obvious necessity for careful proctoscopic examination in cases of rectal bleeding and note that an appreciable number of persons in their series had hemorrhoidectomies during the insidious initial stages of chronic ulcerative colitis. The existence of such a fact is sufficient warrant for the rule obtaining in certain hospitals that a proctoscopic examination must always precede hemorrhoidectomy for rectal bleeding. Such a rule should be applied to general practice, particularly because the performance of hemorrhoidectomy in a patient harboring ulcerative colitis almost invariably lights up the disease and may be responsible for a serious attack.

The results of general bodily depletion associated with ulcerative colitis are fairly well recognized, but several reports are of some interest. Davidson³²⁹ presents observations on 3 patients who had infantilism during the course of the diarrhea incident to serious ulcerative colitis. The potential interference with normal endocrine processes secondary to the deficiency produced by prolonged diarrhea is not generally recognized. Nutritional disturbances, however, are frequently encountered, and it is quite possible that the development of infantilism in these cases in which obviously the patients were in the proper age group—15 to 17 years—was simply another manifestation of nutritional lack, in this case probably some disturbance in the chemistry of the sterones. Clubbing of the fingers is frequently noted, not only with this disease but with regional enteritis and with numerous other chronic nutritional disorders. Schlicke and Baigen³³⁰ presented no new material, however, they emphasize the incidence of this curious manifestation of metabolic deficiency and point out the implication inherent in such a physical finding. Without any question, the finding of clubbed fingers gives a direct indication of the degree of nutritional deficiency that exists as a result of prolonged disease. A most unusual finding is that reported by Rassmussen,³³¹ who notes the occurrence of multiple areas of calcification in the subcutaneous tissue of a patient with ulcerative colitis. The calcinosis developed at the climax of the colonic disease and disappeared in the course of three or four months, coincidentally with considerable improvement in the colitis.

329 Davidson, S. Infantilism in Ulcerative Colitis, *Arch Int Med* **64** 1187 (Dec.) 1939.

330 Schlicke, C. P., and Baigen, J. A. Clubbed Fingers and Ulcerative Colitis, *Am J Digest Dis* **7** 17, 1930.

331 Rassmussen, H. Transient Calcinosis Accompanying Ulcerative Colitis, *Acta med Scandinav* **101** 491, 1939.

As far as treatment is concerned, no new therapeutic measures have recently been evolved. Cheney³³² again reports the efficacy of rather intensive parenteral liver therapy, but his observations lose a great deal of their force when one considers that all of the other usual therapeutic measures, such as dietary supervision, rest and administration of opium, were carried out at the same time, with the occasional addition of a vegetable mucin or of kaolin. That the addition of liver extract to other therapeutic measures may be of real value is not to be doubted, that it has any real effect on the course of the disease, except as a collective measure for the results of the associated depletion, should be very seriously questioned.

Reports on the use of azosulfamide (disodium 4-sulfamidophenyl-2'-azo-7'-acetyl-amino-1'-hydroxynaphthalene-3',6' disulfonate) (oral) and sulfanilamide in the treatment of this disease are of real interest. Brown, Herrell and Bagen³³³ present further observations on the continued use of azosulfamide (neoprontosil) and express the opinion that the drug is of definite benefit in helping to control the disease, urging that it be added to the other measures, although recognizing that the clinical response is not predictable and that the drug is in no way curative. Collins³³⁴ similarly reports beneficial results from the use of sulfanilamide, but he, too, points out the necessity of recognizing the natural history of the disease that must be considered in any evaluation of the success attributable to a given form of treatment. It is highly probable that chemotherapy may prove an important addition to measures available in treating this most serious condition. Whatever results are to be expected, however, will probably be due to the effect of such drugs on the secondary bacterial invasion of the colon which invariably accompanies the condition, rather than to any direct effect on the initial causative factor.

The surgical measures to be employed in the treatment of ulcerative colitis are well recognized, as are the indications for their use. The decision that surgical intervention is necessary in individual cases will always constitute a nice clinical point. It is a matter of some surprise that appendicostomy should still be urged as a proper surgical maneuver. The experience of most older surgeons seems definitely to have been that such a measure is followed by disappointing results. It is therefore with some interest that one notes reports by Welcker³³⁵ and Cushman

332 Cheney, G. Idiopathic Ulcerative Colitis. Effectiveness of Liver Extract in Its Treatment, *California & West Med* **52** 66, 1940.

333 Brown, A. E., Herrell, W. E., and Bagen, J. A. Neoprontosil (Oral) in Treatment of Chronic Ulcerative Colitis, *Ann Int Med* **13** 700, 1939.

334 Collins, E. N. Chronic Ulcerative Colitis. Sulfanilamide and Other Factors in Its Management, *S Clin North America* **19** 1089, 1939.

335 Welcker, A. Ulcerative Colitis Considered from the Surgical Point of View, *Nederl tijdschr v geneesk* **84** 1400, 1940.

and Kilgore³³⁶ advocating early appendicostomy in this disease. In view of previous disappointing results, it is again proper to suggest that the favorable results attributed to such a move may be merely coincidental and secondary to the cyclic changes to be expected in the chronic forms of this disease.

Lymphogranuloma venereum as a cause of serious rectal disease continues to attract attention. The clinical manifestations are generally well recognized, but the report of David and Loring³³⁷ is of interest, as it records 4 cases of chronic involvement in which squamous cell carcinoma developed in the lesions of the disease. Such an occurrence has been noted previously, but it is of some importance as suggesting the effect of long-standing inflammation in the causation of malignant degeneration. The rather unsatisfactory results of treatment of this disease still constitute a major therapeutic problem. These authors added their experience to that of a few others and expressed the belief that sulfanilamide is of benefit, although in no sense specific in its action. A somewhat similar article is that presented by Hebb and his associates,³³⁸ who record apparently successful results following the use of sulfur compounds, sodium sulfanilate and sodium sulfamyl sulfanilate. An enthusiastic report on the results of diathermy in the treatment of stricture of the rectum secondary to lymphogranuloma venereum is recorded by Martz and Foote,³³⁹ and results obtained by Martin and de Lorimier³⁴⁰ after radical therapy are also of interest, although the latter authors are very cautious in alluding to the probable outcome of such measures as applied to rectal lesions. It is evident from the various measures advocated in the treatment of this disease that as yet no specific measures have been evolved, and that carefully controlled studies of the efficacy of the already considered maneuvers are necessary if one is properly to judge their value in attacking such a chronic type of granulomatous disease.

Roentgen Study and Other Diagnostic Procedures—Although a detailed consideration of the roentgenologic literature is beyond the scope of this review, it is proper to allude to certain articles of particular

336 Cushman, G. F., and Kilgore, A. R. Appendicostomy for Chronic Ulcerative Colitis, *West J Surg* **47** 692, 1939.

337 David, V. C., and Loring, M. Relation of Chronic Inflammation and Especially Lymphogranuloma Inguinale to Development of Squamous Cell Carcinoma of Rectum, *Ann Surg* **109** 837, 1939.

338 Hebb, A., Sullivan, S. G., and Felton, L. D. Lymphopathia Venereum Treated with Sulphur Compounds, *Pub Health Rep* **54** 1750, 1939.

339 Martz, H., and Foote, M. N. Stricture of Rectum Secondary to Lymphogranuloma Venereum. Treatment with Diathermy, *J A M A* **114** 1041 (March 23) 1940.

340 Martin, J. I., and de Lorimier, A. A. Roentgen Therapy in Lymphogranuloma Venereum, *Am J Roentgenol* **42** 376, 1939.

interest in relation to gastroenterology. Further experience with the roentgen diagnosis of steatorrhea is presented by Kantor,³⁴¹ who adds observations on 2 additional cases to those reported in the previous year. He reviews the roentgen findings by which he considers that a diagnosis of this condition may be properly made: changes in the bones, faint filling of the gallbladder revealed by cholecystography, evidences of ileal stasis and colonic dilatation and redundancy, and, as a striking feature, the peculiar smooth appearance of the upper part of the small intestine described as the "moulage sign." In addition to the "moulage sign," he noted in 1 case the occurrence of intermittent dilatation with spasm in the loops of the small bowel, previously described by Mackie, Miller and Rhoads. The importance of the present report lies in the fact that Kantor is able to present the postmortem observations in 1 instance. Necropsy in this case revealed complete loss of intestinal valvulae in the areas where the "moulage sign" had been observed. These observations probably constitute the first report in which a detailed description is given of a postmortem examination confirming the characteristic roentgen findings associated with idiopathic steatorrhea. An excellent description of the condition accompanies the article.

For purposes of reference, the article by Weber³⁴² on the roentgen manifestations of non-neoplastic lesions of the small intestine is of value. The author described not only the appearance noted in deficiency states, such as sprue, pellagra and celiac disease, but the characteristic findings of chronic enteritis and diverticulosis.

The diagnostic value of roentgenoscopy in cases of acute mechanical ileus is universally recognized, but the article by Chrom³⁴³ is of particular interest, as the author compares the roentgen observations and the operative findings in a group of 32 patients. In 19 of the cases roentgen examination was made within one hour of operation, and in 16 of these the conditions seen at operation agreed entirely with the abnormalities noted by roentgen examination. He points out that it is generally possible to obtain information regarding the location of intestinal distention by means of roentgen examination of the abdomen without the use of a contrast medium, especially in cases of ileus of the small bowel, although such a method cannot be expected to furnish precise information as to the cause, nature and absolute location of the ileus. In cases of obstruction of the large bowel, in which there is no

341 Kantor, J. L. Further Experience with the Roentgen Diagnosis of Idiopathic Steatorrhea. Report of Cases Including Postmortem Observations in One Case, *Arch Int Med* **65** 988 (May) 1940.

342 Weber, H. M. Roentgenologic Manifestations of Non-Neoplastic Lesions of the Small Intestine, *J A M A* **113** 1541 (Oct 21) 1939.

343 Chrom, S. A. Comparison Between Roentgenologic and Operative Findings in Acute Mechanical Ileus, *Acta radiol* **21** 182, 1940.

contraindication to administration of a contrast enema, it is possible to obtain valuable diagnostic aid not only as to the exact level of the obstruction but in many cases as to its nature

The importance of extra-alimentary causes of abnormalities noted in routine studies of the gastrointestinal tract is fairly well appreciated. Too much importance, however, cannot be attached to the necessity for considering such factors before too didactic an interpretation of the results of roentgen examination as the cause for symptoms referable to the digestive tract has been made. A full summary and discussion of these various factors is to be found in the article by Hubeny,³⁴⁴ which is worthy of consideration simply as a reminder of the intricacies and dangers attending a diagnosis of gastrointestinal disease. A more provocative article of a somewhat similar nature is that by Oppenheimer,³⁴⁵ who discusses acute transient intestinal atony on the basis of roentgen examinations. This author describes findings made in a number of patients who on a single examination revealed evidence of an excessive enlargement of the colon, reported as megacolon. For adequate reasons such a diagnosis was not acceptable clinically, and numerous reexaminations of the patients under consideration showed that the colon was perfectly normal in caliber and tone. In 1 case no clinical diagnosis could be made, although intermittent abdominal symptoms were present. In 2 instances a clinical diagnosis of mesenteric thrombosis was made, and in 3 others the presence of renal calculi was demonstrated by roentgen and urologic examinations. It would seem entirely proper to attribute such transient deceptive roentgen findings to reflex disturbances in intestinal motility.

Because of the frequency with which a gastrointestinal aura is noted in epileptic patients, the observations by Robinson³⁴⁶ are of some interest. One hundred patients with epilepsy were studied by routine roentgen examination of the gastrointestinal tract. Of these, 86 were entirely normal, and in the remainder no uniform abnormalities were noted. It was concluded that the gastrointestinal aura frequently associated with epileptic attacks does not depend on demonstrable gastrointestinal abnormalities.

An interesting roentgen study of perisigmoidal infiltration is that presented by Krogdahl.³⁴⁷ Starting with a short survey of the occurrence and frequency of colonic diverticula, the author proceeds to

344 Hubeny, M. J. Extra-Alimentary Causes of Alimentary Filling Defects, *Radiology* **33** 1, 1939.

345 Oppenheimer, A. Acute Transient Intestinal Atony, *Am J Roentgenol* **41** 575, 1939.

346 Robinson, L. J. Radiologic Gastrointestinal Studies in Epilepsy, *Am J Psychiat* **95** 1095, 1939.

347 Krogdahl, T. Roentgenologic Differential Diagnosis of Perisigmoiditic Infiltrates and Sigmoid Cancer, *Acta radiol* **20** 241, 1939.

describe the roentgen manifestations of peridiverticula and perisigmoidal infiltration, with especial reference to diagnostic differentiation between these conditions and cancer of the sigmoid flexure. The importance of diagnosis of the latter condition is sufficient to warrant careful consideration of this article.

Technical measures devised for the study of normal physiologic activity of the various portions of the gastrointestinal tract or for diagnosis of pathologic disturbances are always of interest. The value of any procedure, however, must always be subject to careful and prolonged scrutiny. An example of the absolute necessity for a critical evaluation of any new method is shown in the recent reports on the use of orally administered phenolphthalein for the detection of ulcerations in the gastrointestinal tract. Studies carried out by five different groups³⁴⁸ all indicate the absolute unreliability of this test. A further instance of such unpredictable results incident to the introduction of a new method is indicated in the reports by Hollander, Penner and their associates.³⁴⁹ These authors described a method for quantitative determinations of phenol red concentration in specimens of stomach contents, in which the dye was used as an indicator of dilution. Application of the method with accurate determinations of the concentration of the indicator gave corrected chloride values that were even greater than three times the isotonic concentration of this ion, a finding which obviously suggested absorption of water from the stomach. Such absorption is unpredictable and tends to introduce an error into the dilution indicator technic which renders it of doubtful value at present.

A relatively new instrumental means of diagnosing gastrointestinal and intra-abdominal disease is peritoneoscopy. The exact clinical value of this method is undoubtedly limited to a very selected group of cases such as are available in large institutions. That such a method is of real diagnostic importance within these limitations is gradually becoming apparent. A review of the results obtained in 100 cases is

348 Suttentfield, F. D. The Proposed Phenolphthalein Test for Gastrointestinal Disease, *M. Ann. District of Columbia* **8** 363, 1939. Slutzky, B., and Wilhelmj, C. M. Phenolphthalein as a Test for Gastro-Intestinal Ulceration in the Experimental Animal, *Am. J. Digest. Dis.* **6** 449, 1939. Notkin, L. J., Kirsch, E., and Albert, S. Note on the Value of Woldman's Phenolphthalein Test for Gastro-Intestinal Lesions, *ibid.* **6** 365, 1939. LeVine, R., and Kirsner, J. B. An Evaluation of the Phenolphthalein Test of Woldman, *Am. J. M. Sc.* **198** 389, 1939. Banks, B. M., and Barron, L. E. Phenolphthalein Test in Gastro-Intestinal Disease, *New England J. Med.* **221** 296, 1939.

349 Hollander, F., Penner, A., Saltzman, M., and Glichstein, J. Secretory Studies in Whole Stomach. The Determination of Phenol Red in Gastric Contents, *Am. J. Digest. Dis.* **7** 199, 1940. Penner, F., Hollander, F., and Post, A. The Use of Phenol Red as a Dilution Indicator in Gastric Analyses, *ibid.* **7** 202, 1940.

presented by Benedict,³⁵⁰ who outlines in detail the indications for use of such instrumentation and the type of information that may be obtained, either by direct visualization or by study of the biopsy material thus obtained. As the dangers inherent in such a method of investigation are almost negligible in the hands of a skilled operator, the more general acceptance of its use in properly selected cases is to be expected. An unusual diagnosis made in this fashion is reported by Ruddock and Hope³⁵¹. These authors, one of whom was the first seriously to advocate the use of peritoneoscopy as a diagnostic procedure, describe their observations in a case of coccidioidal peritonitis. The initial diagnosis, based on peritoneoscopic observation, was probable tuberculous peritonitis, but a final diagnosis of the rare condition coccidioidal peritonitis was made after microscopic examination of the biopsy material.

MISCELLANEOUS CONSIDERATIONS

A variety of relatively unrelated articles have appeared in the gastroenterologic literature during the past year and warrant brief comment. Five separate articles dealing with pain in connection with gastrointestinal or intra-abdominal disease are of diagnostic and physiologic interest. Alvarez³⁵² comments in an editorial on the clinical observations of de Paula, who subjected over 2,000 patients to Libman's test for sensitiveness. This procedure, of course, has been utilized for some years in an attempt to differentiate the degrees of subjective sensitivity of individual patients. His data on patients with ulcer were more or less in accord with those previously reported by Cohn, who, as one would expect, found that patients with ulcer were more sensitive to the Libman test when hunger pain was present than when they were free from symptoms. De Paula was unable to find any marked difference in the complaints in the two groups of hypersensitive and hyposensitive patients. He found silent duodenal ulcers occasionally in patients who appeared to be hypersensitive, and many of the hyposensitive ones complained of pain. He was impressed with the fact that tender abdominal points appeared more frequently in the hypersensitive group than in the other.

Lewis and Kellgren³⁵³ present observations made in recent experiments related to referred pain, visceromotor reflexes and other asso-

350 Benedict, E. B. The Value of Peritoneoscopy in Gastroenterology. Review of One Hundred Cases, *Am J Digest Dis* **6** 512, 1939.

351 Ruddock, J. C., and Hope, R. B. Coccidioidal Peritonitis, *J. A. M. A.* **113** 2054 (Dec.) 1939.

352 Differences in Sensitiveness of Patients with Ulcer, editorial, *Am J Digest Dis* **7** 140, 1940.

353 Lewis, T., and Kellgren, J. H. On the Observations Related to Referred Pain, Viscero-Motor Reflexes and Other Associated Phenomena, *Clin Sc* **4** 47, 1939.

ciated phenomena. Although their results are not entirely in keeping with the observations of others, the conclusions of such careful observers are of interest. The authors believe that there is no special form of pain, referred or otherwise, and no special vasosensoory or vasomotor reflex which is the hallmark of visceral disease. Pain of visceral and of somatic origin cannot be distinguished. Deep somatic and certain visceral structures are supplied by a common set of afferent nerves (including pain nerves), stimulation of which produces similar pain and many similar reflex phenomena. This common system, the authors believe, is responsible for all pain and referred phenomena of visceral disease. Variations in reaction depend chiefly on the strength and duration of the stimulus and on the segmental derivation of the afferent fibers stimulated. Kellgren³⁵⁴ discusses the distribution of pain arising from deep somatic structures, with charts of segmental pain areas. In the observations recorded, segmental areas of deep pain and tenderness have been mapped out by stimulating the interspinous ligaments. An extensive investigation was made of the distribution of pain arising from the various deep somatic structures, and it was found that it presents a gradual transition from pain which is confined to a spot in the region of the structure stimulated to diffuse pain of full segmental distribution. Whether the pain is local or segmental appears to depend more on the depth at which the tissue stimulated lies than on its nature. The authors suggest that the segmental distribution of diffuse pain may be a form of false localization. These studies are of profound physiologic interest and of some practical importance but, as has been noted, are not in close agreement, for example, with many careful clinical observations on so-called somatic pain.

A somewhat different approach to the subject is made by Kinsella,³⁵⁵ who studied the sensibility of the peritoneal surface. He confirms the work of previous observers as to the sensitivity of the anterior parietal peritoneum but apparently found that, in contrast to the invariable pain response noted on stimulation of the anterior parietal peritoneum, the results of stimulation of the posterior parietal peritoneum of the right iliac fossa varied considerably in different persons. In half of 20 subjects studied in this manner no sensation was found, but in the other half stimulation of the parietal surface caused pain, referred in most cases to the right iliac fossa. The mesentery of the appendix was universally sensitive to physical stimuli and pain was referred to the midline in most cases. In 14 of 17 patients operated on for acute appendicitis a clinically tender appendix was squeezed at operation and pain was produced. Kinsella reviews previous work

354 Kellgren, J. H. On the Distribution of Pain Arising from Deep Somatic Structures with Charts of Segmental Pain Areas, *Clin Sc* **4** 35, 1939

355 Kinsella, V. J. Sensibility in Abdomen, *Brit J Surg* **27** 449, 1940

done on somatic and visceral pain and is in agreement with the idea that a difference exists between the two. He also presents evidence in which he attempts to show that viscera may be directly sensitive to pain and tenderness in the presence of certain pathologic conditions, such as peptic ulcer or appendicitis. The conclusions are in no way novel, but the observations constitute a rather valuable addition to the present knowledge of subjective sensations arising from visceral disturbances.

An article by Brule and Garban³⁵⁶ on lumbocrural neuralgias of colonic origin is of interest because of the amplification given to preceding observations of a somewhat similar nature. It has been known for some time, although not sufficiently recognized, that colonic disturbances may cause pain apparently due to conditions involving the spine. The authors bring some apparently satisfactory clinical evidence to indicate that pain due to disease or abnormal disturbances in the colon, such as diverticulitis, may be entirely referred to the lumbosacral area and from there along the distribution of the femorocutaneous or crural nerves. An important point in the discussion is notation of the fact that such pains are extremely transient and may come and go with relative rapidity. The source of their origin is indicated by the fact that they respond much more readily to treatment of the underlying colonic condition than to local measures.

That confusion arises between symptoms due to serious cardiac diseases and those originating in the upper part of the digestive tract is known. The importance of correct differentiation between symptoms of cardiac and of gastrointestinal origin cannot be sufficiently stressed, however, and the difficulties incident to a correct differential diagnosis are frequently so great that they constitute a rather forceful argument against gastroenterology as a strict specialty. Wahlberg³⁵⁷ reports 3 cases of roentgenoscopically demonstrable esophageal spasm secondary to myocardial insufficiency or coronary disease. In these cases the picture was an inversion of that presented by Jones,³⁵⁸ Reid³⁵⁹ and others, who record the occurrence of striking substernal pain with reference down the left arm in younger persons and in those with no electrocardiographic evidences of myocardial involvement. In one of these articles³⁵⁸ a striking instance is recorded of a patient 30 years of

356 Brule, M, and Garban, H. Lumbocrural Neuralgias of Colonic Origin, *Presse med* **47** 1061, 1939.

357 Wahlberg, J. Esophageal Spasm as Cardiac Symptoms, *Acta med Scandinav* **101** 568, 1939.

358 Jones, C. M. The Symptomatology of Diaphragmatic Hernia with Some Notes on Therapy, *Tr Am Clin & Climatol A*, 1940.

359 Reid, W. D. Hiatus Hernia Simulating Cardiac Infarction, *New England J Med* **223** 50, 1940.

age who experienced frequent attacks of angina-like pain spreading to the ring and little fingers of the left hand and bearing no direct relation to exercise. Adequate relief was obtained by the use of belladonna and by proper dietary measures, directed toward diminishing the local irritation of a small diaphragmatic hernia. A more complete list of difficulties of the upper part of the gastrointestinal tract leading to apparent cardiac symptoms is outlined by Rodman³⁶⁰ in an orderly, rather textbook-like discussion of the subject. Confirmation of the intimate correlation between cardiac, esophageal and gastric motor activity is to be found in the clinical and experimental studies of Swalm and Morrison³⁶¹. These authors investigated the behavior of the esophagus and stomach during typical attacks of angina pectoris, and, conversely, attempts were made to demonstrate the occurrence of sudden coronary disturbances associated with acute gaseous distention. Temporary cardiac standstill was observed in 1 patient, apparently following distention of the stomach. In this patient the heart resumed its normal activity immediately on release of the intragastric tension. The authors believe, quite properly, that they have produced evidence of a reflex nature of acute cardiac seizures in attacks of angina pectoris. The fact that 1 patient registered no electrocardiographic changes during anginal paroxysms induced through the digestive tract suggested to the authors that the coronary arteries are not the sole factor involved in the production of anginal pain.

The important influence of abnormal endocrine activity on the digestive tract has been alluded to in an earlier part of this review. Blotner³⁶² contributes one interesting finding in a study of gastric secretion in patients with diabetes insipidus. In 6 cases the author thought that he found increases in the hydrochloric acid and rennin content of the gastric juice. The interesting observation was made that administration of solution of posterior pituitary apparently caused a definite decrease in these secretions. Gastric roentgen studies revealed no abnormality in 3 of the 6 patients, the fourth had a duodenal ulcer. A less conclusive but rather interesting discussion of the digestive disturbances apparently incident to hypophyseal disease is found in a purely clinical article by Morañón and Richet³⁶³.

360 Rodman, J. S., and Leahman, W. B. Some Differential Diagnostic Problems in the Borderlands of Gastroenterology and Cardiology, *Rev. Gastroenterol.* **6** 366, 1939.

361 Morrison, L. M., and Swalm, W. A. Role of the Gastro-Intestinal Tract in Production of Cardiac Symptoms, *J. A. M. A.* **114** 217 (Jan 20) 1940.

362 Blotner, H. Gastric Analyses and Gastric Symptoms in Diabetes Insipidus, *Am. J. Digest. Dis.* **7** 73, 1940.

363 Morañón, G., Richet, C., Pergola, A., and Le Sueur, G. Acute Abdominal Syndromes of Hypophyseal Origin, *Lisboa med.* **16** 589, 1939.

The production of digestive symptoms due to pelvic disturbances is well recognized, but, like symptoms pointing toward cardiac disease, they are at times difficult properly to evaluate. That epigastric distress or other gastric symptoms may divert the attention of the clinician from existing pelvic disease is carefully discussed by Simms and Culley,³⁶⁴ and a careful perusal of their article will provide further proof of this important clinical fact. These authors cite, for example, instances of vicarious bleeding from the gastric mucous membrane and aggravation of organic lesions of the stomach during catamenia, in addition to the more ordinary symptoms anorexia, nausea and vomiting, which frequently occur in association with disease of the pelvic organs.

That profound calcium disturbances in the body occur as a result of prolonged vomiting is well known, but not so well recognized is the fact that renal calcification may accompany pyloric and high intestinal obstruction. Martz³⁶⁵ reviewed the history of the literature on this subject, which includes 46 cases of calcification of the kidney secondary to severe and prolonged vomiting, mostly due to cicatricial ulcers of the stomach and duodenum. The chemical changes involved in such a phenomenon are discussed in detail and appear to provide an adequate explanation for such an unusual occurrence in the light of present chemical knowledge. A further example of the relation between disturbances of the digestive tract and alterations in calcium metabolism, as noted in osseous changes, is commented on by Brown and his associates³⁶⁶. These investigators studied 50 cases of generalized osteoporosis in adults, in 22 of which there were distinct gastrointestinal symptoms. None of the patients showed the chemical changes in the blood associated with hyperparathyroidism, and the authors attempt to lay the blame for the osteoporotic lesions on physiologic alterations in the gastrointestinal tract. Steatorrhea, chronic diarrhea and hyperthyroidism were not present, and the actual evidence for participation of the digestive tract would seem to be highly problematic. As most of the patients were women in the later decades of life, the instances under discussion would seem to fall more properly under the heading of osteoporosis associated with the endocrine disturbances incident to the menopause and subsequent years, described by Albright and others. However, as a generous proportion of the patients had definite gastrointestinal symptoms, the authors correctly concluded that a further intensive study of the subject from the point of view of the physiology

364 Simms, J. R., Jr., and Culley, J. C. Gastro-Intestinal Manifestations of Pelvic Inflammatory Disease, *South M J* **32** 774, 1939.

365 Martz, H. Renal Calcification Accompanying Pyloric and High Intestinal Obstruction, *Arch Int Med* **65** 375 (Feb.) 1940.

366 Brown, C. L., Vogel, R., and Meader, R. P. Clinical Observations on the Passive Relationship of Digestive Tract Disease to a Type of Osteoporosis. *Am J Digest Dis* **6** 628 1939.

of the alimentary tract is warranted. A more convincing set of observations is provided by a series of articles by Meulengracht³⁶⁷ on the occurrence of spinal osteomalacia apparently due to dietary deficiency or digestive disturbances. The first report deals with 6 patients with spinal osteomalacia who had obviously been on an inadequate diet for a long period. The second group describes observations on 8 patients who had lived on a somewhat insufficient diet and who had in addition, gastric achylia. In the third series of patients the diet may have been unbalanced but these patients are of particular interest because a careful history revealed the continued excessive use of laxatives. The subjective symptoms experienced by these patients consisted in pain in the back and loin associated with demonstrable change in the vertebral column. The author thinks that he is correct in regarding osteomalacia as a result of dietary deficiency, especially an insufficient amount of or an insufficient proportion between calcium, phosphorus and vitamin D. In this connection he cites the work of several investigators who state that the diet of the Danish population is deficient in calcium, phosphorus and vitamin D, a rather surprising observation about a people who are well supplied with dairy products and whose general standard of living is commonly thought to be high. The proposed relation between improper calcium, phosphorus and vitamin D absorption and gastric achylia and a consequent improvement of the increased intestinal activity due to the excessive use of laxatives would seem to be entirely reasonable.

Two rare and possibly closely related cases involving a faulty utilization of fat are reported by Reinhart and Wilson³⁶⁸ and by Tannhauser and Davidson³⁶⁹. The first case, recorded by Reinhart and Wilson, is designated as one of intestinal lipodystrophy similar to that first described by Whipple. The early clinical manifestations were predominantly those of a blood dyscrasia, and a tentative diagnosis of pseudoleukemia was made. Subsequent chylous ascites developed, and an obstruction of the thoracic duct due to lymphadenosis was postulated. Fatty diarrhea was not a prominent clinical symptom. Subsequent examination at section revealed a massive deposition of fat in the sinuses of the mesenteric and retroperitoneal lymph nodes associated with emaciation. The evidence suggests abnormal excretion of fat into the intestinal canal, with increased reabsorption and subsequent deposition into the lymph nodes. The case reported by Tannhauser and Davidson

367 Meulengracht, E. Spinal Osteomalacia from Deficient Diet or Disease, *Acta med Scandinav* **101** 138, 1939.

368 Reinhart, H. L. and Wilson, S. J. Malabsorption of Fat. Intestinal Lipodystrophy of Whipple, *Am J Path* **15** 483 1939.

369 Tannhauser, S., and Davidson, R. Gastro-Intestinal Pseudoleukemia. Report of Case. *Am J Digest Dis* **7** 45 1940.

was one of massive fatty diarrhea associated with anemia, emaciation and weakness. In this instance active disease of the liver appeared to be present in view of an increased output of urobilinogen in the urine, a reduction in cholesterol esters, an impairment in galactose tolerance, a reduced albumin-globulin ratio and an increase in plasma fibrinogen. A low level of blood calcium (7 mg per hundred cubic centimeters) was observed, apparently associated with the fatty diarrhea. Innumerable small nodules were demonstrated throughout the intestinal tract by roentgen examination, suggesting either polyposis or, more probably, gastrointestinal pseudoleukemia.

A much more common type of fat intolerance is that noted in cases of celiac disease, 73 of which were observed by Hardwick³⁷⁰. The diagnosis was established by the classic clinical features, diarrhea, anorexia, loss of weight and an excess of normally split fat in the stools in more than one case. The study is of value because of the long time during which the patients were observed. Twenty-two died in the hospital, but all but 10 of the remainder were traced, 17 appeared to have recovered clinically and biochemically for more than three years, and 10 others had been free from symptoms for a somewhat shorter period, a total of more than one third of the entire group. That the absence of clinical symptoms did not imply complete inactivity of the disease was indicated by the fact that 4 patients thought to be well still showed steatorrhea and were considered to be in the quiescent phase of the disease. The author implies that idiopathic steatorrhea of adults represents merely reactivation of celiac disease acquired in early life.

Still another instance of recurrent diarrhea with evidences of hepatic dysfunction, leukopenia and megalocytic anemia is reported by Nordenson³⁷¹. He compares the condition to nontropical sprue, and one is led to speculate as to the possibility that it may be related to the condition in the case reported by Tannhauser, just alluded to. The point of interest is that the case is reported under the subject of atrophy of the spleen.

Minor gastrointestinal symptoms caused by allergic disturbances are common, although recognition of them is not always easy. The appearance of such acute abdominal emergencies as those represented by the attacks noted in patients with Henoch's purpura and angioneurotic edema serve to emphasize the occasional importance of recognizing an allergic mechanism as the major factor in serious upsets of the digestive tract. The mechanism underlying the local production of acute pain or distress under such circumstances has always been considered to be

370 Hardwick, C. Prognosis in Celiac Disease. Review of Seventy-Three Cases, *Arch Dis Childhood* **14** 279, 1939.

371 Nordenson, N. G. Atrophy of the Spleen, *Nord med (Hygiea)* **4** 3342, 1939.

partial obstruction due to sharply localized edema, and a moderate number of observations obtained at laparotomy are available to support such a view. Further proof that such a conception is logical was presented by Withers,³⁷² who attempts to explain the symptom experienced by some allergic patients—difficulty in swallowing—on the basis of an esophageal reaction. Examination of the esophagus by means of the esophagoscope apparently revealed localized edema of the mucous membrane of the esophagus and smooth muscle spasm. The variety of allergens capable of producing symptoms continues to grow in number, particularly with the increased use of various new chemical products. An example of this is contained in the report by Hecht and his associates³⁷³ of a case of generalized facial erythema and abdominal distress characterized by cramps, frequent bowel movements associated with increased mucous secretion and pencil-like stools. Careful study revealed that the case was one of contact dermatitis and gastrointestinal allergy due to tetrabromofluorescein contained in a lipstick used by the patient.

Although the causal relation between lead poisoning and acute abdominal symptoms is well known, the report of Otto and Kuhlmann³⁷⁴ is of some interest. The authors describe the usual and well recognized manifestations of lead colic, together with the equally well recognized roentgen findings of increased tone and spasm in the small intestine. In addition, however, attention is directed toward a phase of the gastrointestinal manifestations of lead poisoning that is not generally recognized, namely, esophageal disturbances. Abnormal esophageal disturbances, the authors imply, are more frequent than is commonly supposed and consist of symptoms of retrosternal pressure, pyrosis and, in rare cases, regurgitation. Spasmodic contractions and even paralysis of the esophagus have been observed as a result of lead poisoning. Attention is also directed to the existence of inflammatory changes in the wall of the stomach as an associated finding in cases of lead intoxication, with the occasional presence of gastritis and gastric ulcers. It has been pointed out by a few observers that the gastric manifestations of this disease may predominate and that the associated roentgen findings may closely simulate those of carcinoma of the stomach. In this regard the report by Magnuson and Raulston³⁷⁵ is of interest. Eight cases of

372 Withers, O. F. Gastro-Intestinal Allergy, with Special Reference to the Esophagus, *South M. J.* **32** 838, 1939.

373 Hecht, R., Rappaport, B. Z., and Bloch, L. Cheilitis, Fixed Drug Eruption and Gastrointestinal Allergy for Eosin Dye of Lipstick, *J. A. M. A.* **113** 2410 (Dec. 30) 1939.

374 Otto, H., and Kuhlmann, F. Behavior of Gastrointestinal Tract in Lead Poisoning. Intestinal Disturbances, *Klin. Wchnschr.* **18** 1081 1939.

375 Magnuson, H. J., and Raulston, B. O. Lead Poisoning in Roofers, *J. A. M. A.* **114** 1528 (April 20) 1940.

lead poisoning in roofers are reported. The patients had been working as roofers for periods varying from three months to ten years and gave a history of holding the galvanized roofing nails in their mouths while working. None gave a history of any other exposure to lead, and none had had lead colic prior to May 1939, at which time a new type of nail was used. This particular nail was shown to be the source of the lead poisoning, which caused symptoms of colic in all and constipation in the majority of workers. One had neuritis, and a lead line was present in 5 of the 8 cases. In 1 instance there were early signs of hypertension. The blood picture was characteristic. Of particular interest were the diagnoses made on admission of the patients to the hospital, which were correct in only 3 instances, the diagnoses in the other 5 cases being peptic ulcer, cancer of the stomach or appendicitis.

A cause of acute abdominal pain which is unusual, at least to physicians practicing in northern latitudes, is recorded in the report by Daniel³⁷⁶ of a study of 266 cases of malaria. Nine of the patients in this group had attacks simulating acute abdominal disease, and 6 were admitted to the surgical service for emergency treatment. The abdominal pain was accompanied with nausea and vomiting and in several instances increased steadily in severity. There was definite involuntary spasm of the abdominal wall at the time of admission in 3 patients. The spleen was palpable in only 1 case. Malaria was suspected, and the diagnosis was finally established because of initial leukopenia in 2 cases, a rise in temperature accompanied by leukopenia at some time after admission in 3, the occurrence of an unexplained chill in 2 others and the finding of parasites in routine smears of blood in the remainder. Although malaria occurs with relative infrequency in northern clinics, the increase in travel to malaria-infested countries in recent years makes such a report of interest and importance at present.

An unusual manifestation of myelogenous leukemia is that reported by Jones,³⁷⁷ who describes a case of this disease from the point of view of the hematologist. The unusual feature was the appearance of extensive ulceration of the small bowel, the ulceration being at the site of myeloid infiltration but affecting all layers of the intestinal wall. One of the ulcers perforated, causing peritonitis.

376 Daniel, R. A. Malaria Simulating Acute Surgical Diseases of the Abdomen, *Ann Surg* **111** 436, 1940.

377 Jones, E. E. Intestinal Ulceration in Myelogenous Leukemia, *Lancet* **1** 174, 1940.

Correspondence

WIRE LOOP LESIONS

To the Editor —In an article by Dr. Harry Keil entitled "Dermatomyositis and Systematic Lupus Erythematosus. II. A Comparative Study of the Essential Clinicopathologic Features," in the August issue (*ARCH INT MED* **66** 339, 1940), the author gives me the credit (in footnote 4, on page 342) for the term "wire loop lesions" used to describe manifestations observed in lupus erythematosus.

Dr. G. Baehr first observed the so-called "wire loop lesions" in the glomeruli in a case of lupus erythematosus in 1921. The autopsy protocols of the Mount Sinai Hospital in that year record the fact that he had already determined that the peculiar material in the capillary walls was not related to amyloid. Shortly after I joined the staff of the Hospital in 1927 as pathologist, he discussed with me his observations of glomerular and widespread vascular lesions in connection with a patient who came to autopsy about that time. When additional clinical and pathologic material became available in 1930, he and I, in collaboration with Dr. Schiffrin, restudied all the clinical and pathologic material of the preceding years.

PAUL KLEMPFNER, M.D., Pathologist, Mount Sinai Hospital

Book Reviews

An Introduction to Medical Mycology By George M Lewis, M D, associate and assistant attending dermatologist, New York Post-Graduate Medical School and Hospital, Columbia University, instructor in medicine (dermatology), Cornell University, attending dermatologist to St Clare's Hospital, visiting dermatologist to Welfare Hospital, and Mary E Hopper, M S, assistant in mycology, Skin and Cancer Unit, New York Post-Graduate Medical School and Hospital, Columbia University Price \$5.50 Pp 315 Chicago The Year Book Publishers, Inc, 1939

The clinical pathologist has received any monograph or book on the subject of medical mycology with hope, at least, the dermatologist, with apprehension. Up to the present the subject certainly has been in a chaotic state, and fundamental research is needed perhaps as urgently in this field as in any field of laboratory diagnosis.

This book does much to simplify the subject, chiefly by giving a series of emphatically positive statements concerning the laboratory diagnosis of mycologic diseases. It places the clinical side of the subject, so far as present information is concerned, within the reach of dermatologists and those general practitioners who desire to do more than prescribe ammoniated mercury and calamine lotion for every affliction of the skin. The first part of the book has a brief historical summary and a few cursory statements concerning classification, structure, physiology and methods of diagnosis. There is an adequate chapter on the trichophyton test, with reports of original observations, and this is followed by a similar, and naturally less comprehensive, chapter on the oidiomycin test. There are some minor discussions of allergic manifestations of immune bodies, and then the real meat of the book begins.

The first of these important sections deals with superficial mycoses, and certainly the illustrations will delight any practitioner of medicine, even if he has passed the dermatologic board. The section on deep mycoses is more superficial, and one finds no reference to *Histoplasma* or to the clinical manifestations of infections with *Alternaria*.

The last section of the book deals with laboratory diagnosis, and here there are, again, magnificent illustrations of the gross and microscopic characteristics of various fungi which are commonly encountered. The descriptions which are given of twenty-two fungi are brief and are more dogmatic than would be considered discreet in the light of present knowledge. For instance, the statement in reference to immune reactions in actinomycosis will need considerable amplification for any one to make use of it, especially since no reference is given to the original work on the subject. The basic medium for isolation of fungi is one modified by Weidman from the Sabouraud formula and will be found to be generally useful.

The format of the book is characteristic of what will be called "fine book-making." The paper is of the best quality and the type face is extremely legible. However, there is a tremendous amount of waste space in the headings and at the end of chapters, this will not detract from the value of the book except for those whose habit it has been to save.

The material issued to advertise this work makes much of "athlete's foot," but the title is not in the index. However, the subject is discussed in the text under its more scientific name.

There is no question that this book will be favorably received by laboratory workers and clinical practitioners alike and that it will serve as a useful guide to both groups.

La mielosì eritemica acuta (malattia di Guglielmo) By Angelo Baserga with a preface by Adolfo Ferrata Pp 218 Pavia Tipografia gia Cooperativa, 1938

Hematologists in the United States are familiar with several syndromes in which large numbers of immature red cells are found in the blood and which appear to be definite dyscrasias of the erythropoietic system Erythroblastosis foetalis and Cooley's erythroblastic anemia are cleancut entities, and the von Jaksch syndrome is less definite Remarkable outpourings of nucleated erythrocytes and their precursors are observed in the "myeloid reaction" incident to the metastasis of malignant growths to the marrow This has been called "leukanemia" In Lederer's acute hemolytic anemia and in the hemolytic crises of familial hemolytic icterus many nucleated red cells may be found in the blood films The Italian hematologists, however, seem to have a corner on a series of disorders described by them as erythremic myeloses These disorders are classified as intergrades between erythroblastosis foetalis, which they designate as *mielosis eritemica acutissima*, and Cooley's anemia, which is called *mielosis eritemica chronica* The specific disorder discussed in this monograph is the *mielosis eritemica acuta*, or the "disease of Di Guglielmo"

This monograph exhaustively presents some 30 cases of "erythroblastemia" from the Italian literature, in 17 of which the condition is said to be acute erythremic myelosis The concept that there should be such a disease apparently of a leukemia-like character is not illogical if the proposition is agreed to that erythroblastosis foetalis is a neoplastic, leukemia-like disorder With this granted it is reasonable to expect various erythroblastic anomalies to coincide with the different types of myeloid leukemia, the severity of which varies with the stage of development of the granulocyte involved In the pathologic studies of these conditions the different authors have sought the "hiatus leukaemicus" which Naegeli taught defined a leukemia, and have found one with surprising regularity

The difficulty with the entire subject is that none but Italian hematologists see such conditions Even Prof Ferrata, in his preface, states that he has seen none, except that of Di Guglielmo's case, and he does not comment on the accuracy of the diagnosis in that instance The author of the monograph offers no explanation for the peculiar incidence of the disease However, a skeptical survey of the case reports is illuminating Four of the patients had congenital syphilis, and the state of the blood in the majority of the rest is not noted One patient had a lymphosarcoma, the conditions of 3 sound much like examples of Lederer's anemia, with their brief three to five day courses On only about half the patients was an autopsy performed, although biopsies of material taken from the bone marrow were made for most of them Several of the patients were seen but once in pediatric dispensaries, had but one blood count and perhaps a splenic puncture performed, and then disappeared and were not followed up

One is forced to wonder whether Prof Ferrata never saw any such conditions because he called them by other—and more correct?—names Is this perhaps why none have been seen in England and America? Or is there some peculiarity of the Italian bread and soil which produces these dyscrasias? The reviewer believes that Baserga's publication is too shaky a foundation to carry the weight of a new and distinct disease entity

Roentgen Technique By Clyde McNeill, M D Price, \$5 Pp 315, with 267 illustrations Springfield, Ill Charles C Thomas, Publisher, 1939

As is mentioned in the foreword, the book deals chiefly with the ways of exhibiting anatomic structure roentgenographically This implies, of course, that roentgenographic interpretation must be given due consideration if the technical problem of roentgenography is approached intelligently Essentially Dr McNeill's book is a complete atlas of the positions used in roentgenographic procedures Each procedure is illustrated with a halftone reproduction of a photograph showing the position of the anatomic structure under discussion in respect to the roentgen

tube and the roentgenogram, and in most instances a line drawing of the roentgenogram thus produced is substituted for the roentgenogram. A short description of each procedure accompanies the illustrations.

The book is well constructed in all respects. The index is adequate and the bibliography as extensive as the subject matter demands.

Much interesting and practical material has been collected here. It is probable that Dr. McNeill's book will prove to be of quite as much value to the roentgenologist as it is to his roentgenographer.

Micro-Diffusion Analysis and Volumetric Error By Edward J. Conway, M.B., D.Sc. Price 25s. Pp. 306, with 49 illustrations. London: Crosby Lockwood & Son, Ltd., 1939.

Ninety pages are devoted to the study of the error in volumetric titration, and can be of interest only to an occasional professional analyst. The apparatus, principles and practice of microdiffusion analysis are discussed for 186 pages; these will be of interest to the biochemist, but the methods will probably not supplant those already in use in the clinical laboratories of this country.

An appendix of 15 pages discusses the measurement of renal function from the standpoint of a general diffusion-pressure equation derived from previously published data and a consideration of the formula for estimation of renal work. This section will interest the physiologist but not the clinician.

Peripheral Vascular Diseases: Diagnosis and Treatment By William S. Collens, B.S., M.D., and Nathan D. Wilensky, M.D. Price, \$4.50. Pp. 243. Springfield, Ill., and Baltimore: Charles C. Thomas, Publisher.

This volume is intended by the authors to give ready reference to information concerning the diagnosis and treatment of arterial diseases. There is an excellent chapter on the general principles of therapy of arterial diseases and many details in regard to the management of specific disorders are also given. This portion of the volume is particularly good, for it emphasizes those methods with which the authors have achieved their best results. Intermittent venous compression occupies a very important place and probably rightly so.

The sections on methods of examination and on the general symptomatology of vascular diseases are especially well done, as are the articles on peripheral vascular sclerosis and thromboangitis obliterans. The writers have obviously had their most extensive experience with these disorders. The section on the diagnosis of vasospastic diseases is the weakest portion of this work.

Die Ischias By Dr. Hans-Georg Scholtz. Price, 4.87 marks. Pp. 111, with 24 illustrations. Dresden: Theodor Steinkopff, 1939.

This booklet, sixteenth in a series on rheumatic infections edited by Dr. Rudolf Jurgens, is devoted to the subject of sciatica. After a short general discussion on what is understood about the disease, the author deals with the anatomy of the sciatic nerve. The pathogenesis of the disease is considered from many angles, with the conclusion that there is not one etiologic factor, but many. The discussions of symptomatology and diagnosis are followed by a short chapter outlining, in a most practical way, the method of examining a patient whose complaint is sciatic pain. The next chapter, which constitutes over half of the booklet, is allotted to treatment. Great weight is placed on Eppinger's use of aminopyrine in small doses; the author strongly recommends such therapy when the disease is in the acute state. Stress is placed on such measures of physical therapy as baths, heat in all forms and massage. The last two chapters are devoted to prognosis and prophylaxis.

The book is intended, as the author states in the foreword, to aid the German physician in his daily work. It is made as practical as possible and is based on the experience of four years during which the author treated 400 patients ill with sciatica. There are many illustrations. The author's style is an easy one, making for enjoyable reading.

A Textbook of Bacteriology By Hans Zinsser, M D, and Stanhope Bayne-Jones, M D Eighth edition Price, \$8 Pp 990, with 116 illustrations New York D Appleton-Century Company, Inc, 1939

Every reviewer who comments on a book that has gone through many editions always makes the statements that this is another book which has stood the test of time and that a new edition requires little or no discussion These broad statements may well be applied to the eighth edition of the standard textbook of bacteriology of which Hans Zinsser is the senior author

The book is packed with information, not only technical in nature but also broad in character, and is most instructive for the public health worker, the internist or, as a matter of fact, any one who is in actual contact with disease

In the preface to this new edition the authors list the many changes that have been made in the text as a result of the "rapid advances in bacteriology and immunology during the past few years" The section on pathogenic protozoa has been omitted, the authors modestly claim that neither is competent to write on protozoology A small amount of redundant material has been deleted, some new illustrations have been added The whole book is smaller in size than the last edition

This text is too well done to need fulsome praise Its authors are so competent and so well qualified in their branch of medicine that their opus is without doubt the best book of its kind on the booksellers' shelves

Maladies de l'intestin Volume IV By R Bensaude, with the collaboration of A Cam, A Lambling, J Rachet, A Bensaude, F Bertillon, Massot, and E Sidi Price, 90 francs Pp 374, with 97 illustrations Paris Masson et Cie 1939

This is the fourth volume of a series on "Diseases of the Intestine" prepared by R Bensaude with the aid of many collaborators This volume includes a discussion of hemorrhoids, anal fissures, pruritus ani, hemorrhoids and angiomas in infants, hemorhagicopuulent rectocolitis, inflammatory rectal strictures and anorectal actinomycosis Each subject is presented in the usual fashion, including discussion of etiology, pathology, diagnosis, treatment and the like All chapters are well illustrated More than half of the monograph is devoted to a discussion of hemorrhoids

The material is presented more from a practical medical point of view than from a surgical one The authors include very little bibliographic data most of the material being based on their own observations, and they present nothing particularly new Nevertheless, the simple and practical discussions of their personal experiences, which are based on the clinical methods used in France probably justify this volume, particularly from an American point of view This monograph should prove of some value to proctologists and gastroenterologists who, as specialists, are well acquainted with most of its contents To the French-reading physician in general practice the work should be of very real worth

Nitrous Oxide-Oxygen Anesthesia By F W Clement Price, \$4 Pp 274 Philadelphia Lea & Febiger, 1939

The great progress that has been made in the past few decades toward perfecting general anesthesia and especially nitrogen monoxide-oxygen anesthesia has been due in great part to the splendid achievements of the late Dr E I McKesson It is indeed fortunate that the accomplishments, "the teachings and the findings of the 'Master' as well as his own impressions and experiences" are preserved particularly by one who was "his friend, partner and co-worker"

The book is divided into six parts, the first of which considers the theories and signs of nitrogen monoxide-oxygen anesthesia The second and the third part are concerned primarily with the general and special techniques of administration and the advantages and disadvantages of the method The fourth part deals with its use in the various types of operative procedures The employment of the

method for dental anesthesia and analgesia is presented in the fifth part, and the physical factors in the administration of gaseous anesthetic agents are discussed in the sixth part

The book is written in a clear, concise and pleasant style. A summary is presented after each chapter. The seventy illustrations are not only apt and instructive but also well reproduced. The value of the book as a reference would have been considerably enhanced by the inclusion of a bibliography. However, it will serve as an excellent, practical and instructive guide not only to those interested in this specialized field but to all surgeons.

The Neurogenic Bladder By F. C. McLellan, M.D., Instructor in Surgery, University of Michigan. Price \$4. Pp. xvi + 206, with 49 charts, 8 figures and frontispiece. Springfield, Ill., and Baltimore. Charles C. Thomas, Publisher, 1939.

This monograph is well worth knowing. It is not long, its bulk is due largely to the appendix and charts. Into one hundred and thirteen pages of solid reading, however, is packed all manner of information, novel to the ordinary clinician, concerning the bladder and its functions.

The author discusses the anatomy, physiology and pathologic physiology of the bladder interestingly and with spirit. He shows that the bladder is a reflex organ, that the bladder reflex, like any other reflex, can be determined and that this reflex is of great importance in neurologic diagnosis, and, finally, he explains how the bladder reflex can best be studied, what cystometry is and how the results of cystometric study are to be interpreted.

There is a bibliography of 118 references at the end of the book, covering the ground from T. R. Elliott's studies of 1907, on the innervation of the bladder and urethra, to the present. The history of the development of knowledge relating to the bladder reflex is of itself worth reading. There is also an adequate index, conveniently arranged for him who wishes quickly to learn anything of the bladder and its anatomy, of cystometry, or of the behavior of the bladder in traumatic myelitis or under a variety of other circumstances. On the whole, the author is to be congratulated. He has put together, attractively, a useful, interesting and informative volume.

Office Gynecology By J. P. Greenhill, B.S., M.D., F.A.C.S. Price \$3. Pp. 397, with illustrations. Chicago. The Year Book Publishers, Inc., 1939.

There has been a marked need for a volume of this type. The majority of general practitioners are not interested in operative gynecology but are intensely interested in office or medical gynecology, which constitutes a large part of their practice. This volume, containing three hundred and ninety-seven pages of clear, concise, interesting subject matter and one hundred and six excellent illustrations, more than meets this demand. Each chapter, whether on cervicitis, vaginitis, sterility or some other gynecologic problem, contains detailed information of practical value. Methods of diagnosis or treatment necessitating hospitalization or expensive equipment are not discussed. Of especial value are the chapters on postpartum care, premarital advice, sterility and contraception. This volume is highly recommended to the general practitioner and should be of inestimable value to him.

Simplified Diabetic Manual By Abraham Rudy, M.D. Second edition. Price, \$2. Pp. 216. New York. M. Barrows & Company, Inc., 1940.

This is a helpful book for the patient, nurse or doctor who seeks up-to-date information on the treatment of diabetes with diet and insulin. The second edition carries an introduction by Frederick M. Allen, who comments on the soundness of the author's method and congratulates him on avoiding fads and reckless extremes of treatment. The dietary part of the book is especially valuable, because of the attention paid to taste and food habits of various nationalities. Italian, Armenian and Jewish. Commendable attention is given to the nutritional adequacy of diets.

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DIABETES MELLITUS AND SYPHILIS

A STUDY OF TWO HUNDRED AND FIFTY-EIGHT CASES

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The relationship of diabetes mellitus and syphilis occurring in the same patient has for several decades been a frequent subject of discussion by clinicians in all countries. In the latter part of the nineteenth century much was written to the effect that syphilis was either the sole cause or a frequent cause of diabetes mellitus. Many physicians considered diabetes mellitus to be a so-called parasymphilitic disease. The discovery and adoption of serologic tests rapidly dispersed notions of parasymphilitic diseases, and the application of laboratory tests for determination of urine and blood sugar values greatly clarified the situation found in true diabetes mellitus.¹

Two excellent papers concerning this problem have appeared in the literature. Labbé and Toufflet,² in France, and Lemann,³ in the United States, thoroughly discussed the subject. In addition, Rosenbloom⁴

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1 The subsequent use of the word "diabetes" alone is to apply only to diabetes mellitus, and the word "diabetic" is used in reference to patients having diabetes mellitus.

2 Labbé, M., and Toufflet, H. Le rôle de la syphilis dans l'étiologie du diabète, *Ann de méd* **13** 367-382 (April) 1923.

3 Lemann, I. I. The Relations of Syphilis and Diabetes to One Another, *Am J Syph* **13** 70-112 (Jan) 1929.

4 Rosenbloom, J. A Study of the Relation Between Syphilis and Diabetes Mellitus, *Am J Syph* **5** 634-642 (Oct) 1921.

reviewed the literature and listed many references. In neither the generally used American medical textbooks nor the systems of medicine is there, however, more than an occasional comment on coexistent diabetes and syphilis. Of the syphilologists, Stokes⁵ and Moore⁶ both comment briefly on the subject and are in accord, the latter stating that though syphilitic diabetes is a great rarity, the association of diabetes and syphilis is frequent.

The primary purpose of this paper is the analysis of 258 cases of proved true diabetes mellitus, in which there is also proved evidence of syphilis.⁷ So far as we know this is by far the largest group reported in the literature. Such a study we regard as being of much value, as contrasted with the large majority of isolated reports in the literature in which there are only meager details and short follow-ups of a single case or of a few cases, with the result that the cases are entirely inadequate for a proper evaluation. If syphilis, which is a disease supposed to infect eventually "1 in 10" people in this country, has any etiologic relationship to diabetes, a disease which has become the ninth chief cause of death in this country, we know that a study bringing any light on this possible relationship will be of value, and therefore we present our large series of cases which have been subjected to close critical analysis. Incidentally, though the fact does not necessarily signify any relationship between syphilis and diabetes, of all the countries in the world, only in Norway (and to a less extent in certain other Scandinavian countries) has there been a reduction in diabetic mortality in recent years, and in a similar period in Norway the incidence of syphilis has been reduced 90 per cent.

CRITERIA FOR ASSUMING THE EXISTENCE OF SYPHILITIC DIABETES

Various authors generally mention the 4 postulates given by Troller⁸ which must be complied with before diabetes may be assumed to be the result of a syphilitic infection.

- 1 Diabetes must appear subsequent to the syphilitic infection
- 2 Diabetes should appear at the same time as other syphilitic manifestations

5 Stokes, J. H. *Modern Clinical Syphilology*, Philadelphia, W. B. Saunders Company, 1934.

6 Moore, J. E. *The Modern Treatment of Syphilis*, Springfield, Ill., Charles C. Thomas, Publisher, 1933.

7 This paper was originally prepared not only as a report of our own cases but also as a review of the literature. Because of the resultant great length it has been greatly condensed.

8 Troller, D. *Essai sur le diabete sucré syphilitique*, Thesis, Paris, no. 138, 1905.

3 Antisyphilitic treatment alone should cause the disappearance of both the syphilis and the diabetes

4 Antidiabetic treatment alone should be ineffective

Kitchell⁹ made important comments on these postulates. He pointed out that proving the first postulate is difficult, as the symptoms of syphilis may be overlooked in the patient until the more distressing picture of diabetic acidosis supervenes. Regarding the second postulate he pointed out that in these days of serologic diagnosis of syphilis it is not necessary to have syphilitic manifestations to make a diagnosis of syphilis. As regards the third postulate, adequate antisyphilitic treatment should result in a fairly prompt improvement of syphilitic diabetes and should be ineffective on diabetes not caused by syphilis. Failure in the antisyphilitic treatment of some authors has led them to conclude wrongly that the diabetes did not improve because of the permanency of pancreatic fibrosis produced by syphilis. Though such a state could be possible if syphilis does cause diabetes, it is certainly a great mistake to apply such a blanket-like presumption to all cases. One must not forget that it is perfectly possible that both diabetes and syphilis can be coexistent diseases without any pathologic relationship whatsoever. It is only reasonable that for proof of the third and fourth postulates the patient should be on a standard regimen. Certainly a patient should be in a state in which the glycoregulatory mechanism and balance are as constant as possible, that constancy being brought about with diet and with insulin if necessary. Then only should antisyphilitic treatment be introduced. When these conditions have been fulfilled and if there is disappearance of the diabetes or evidence of marked improvement, one might rightfully conclude that the syphilis was related to the diabetes and that antisyphilitic treatment cured or ameliorated the diabetes. As early as 1906 Naunyn¹⁰ pointed out that the mere fact that a diabetic patient improves with antisyphilitic treatment is not too significant, because a diabetic patient will improve with treatment of any complicating coexisting disease. Furthermore, even if the diabetes does improve with treatment of the syphilis, it does not mean that syphilis caused the diabetes unless the other manifestations of syphilis in the body also improved. Practically no case in the literature fulfils these requirements even in small part. The various authors pay little or no consideration to (1) the fact that antidiabetic treatment is frequently instituted simultaneously with the antisyphilitic treatment, either purposely or unwittingly, (2) the quick response that many diabetic patients make with the first antidiabetic treatment, (3) the very important factor

9 Kitchell, J. R. Syphilitic Diabetes, *Pennsylvania M. J.* **41** 587-589 (April) 1938

10 Naunyn, B. *Der Diabetes mellitus*, Vienna, Alfred Holder, 1906

of the reduction of weight, commonly overlooked in the amelioration of diabetic symptoms, and (4) the even more important factor that cases must be followed for a long period, even several years, as will be subsequently described in our criteria for cure

PATHOLOGIC CHANGES

Pancreas—Syphilis might produce diabetes in a variety of ways, and naturally the first way that comes to mind concerns involvement of the pancreas. Boyd¹¹ in a few lines summarized the situation

In congenital syphilis the pancreas often contains large numbers of spirochetes. The acini are poorly developed, their place being taken by cellular connective tissue. Acquired syphilis [in the pancreas] is uncommon and usually takes the form of diffuse fibrosis. A gumma of the pancreas is extremely rare.

It is unlikely that an isolated gumma could ever produce diabetes. Probably only a generalized sclerosis nearly destroying the whole pancreas could be the cause of diabetes. The islands of Langerhans are affected in two ways. The most important is perivascular and interstitial fibrosis, but there is also obliterative endarteritis. Destruction of the islands is one of the last changes to be brought about. Accordingly, it would seem improbable that diabetes could be a manifestation of early syphilis, and it would be unlikely even in the so-called secondary stage. Because of the nature of the destruction of the islands, it is improbable that return of function could occur after institution of antisyphilitic therapy. Regeneration of the islands is known to take place, as Warren has shown in islands damaged by agents other than syphilis, but in an old syphilitic process, which is more of a chronic choking process in contrast to an acute toxic agent, it is not likely that regeneration would occur during the course of antisyphilitic therapy.

The observations of Warthin¹² have for years received little consideration and have never been confirmed, but at the time of their presentation they seemed so important in the problem of combined syphilis and diabetes that they must be presented. In 11 of 12 cases of diabetes coming to autopsy, he found changes which he attributed to syphilis. No other pathologist has been able to confirm similar observations. Warthin did not assert that diabetes was the result of syphilis but stated:

If it is true that a chronic interstitial pancreatitis is the most common pathological finding in the pancreas in diabetes, it seems very likely that syphilis is

11 Boyd, W. A Textbook of Pathology, ed. 3, Philadelphia, Lea & Febiger 1938.

12 (a) Warthin, A. S., and Wilson, V. The Coincidence of Latent Syphilis and Diabetes, *Am J M Sc* **152** 157-164 (Aug.) 1916. (b) Warthin, A. The New Pathology of Syphilis, *Am J Syph* **2** 425-452 (July) 1918.

the most common cause of interstitial pancreatitis, but not necessarily the only cause. Syphilitic pancreatitis may be a common cause of diabetes if it can be shown that interstitial pancreatitis is the essential pathology of diabetes.

Liver—Labbé and Touffet² discussed the possibility of syphilis being able to produce enough damage in the liver to cause a kind of diabetes and disproved the cases they collected in the literature. Certainly such cases must be very rare. A case of this sort would not be one of true diabetes mellitus but rather an instance of a type of glycosuria resulting from inability to store dextrose properly in the liver.

Nervous System—It is possible that syphilitic involvement of the brain and the hypophysial region could produce glycosuria, but this might not be true diabetes. Other than the meningitis there could be arterial involvement in the nerve tissue. Changes produced in the brain or medulla or spinal cord might in some way interfere with the neurologic part of dextrose metabolism. Various authors¹³ discuss possible cases, but none of the cases are conclusive. Proof of such disturbances would be almost impossible to give. Transitory glycosuria sometimes found with various types of lesions of the central nervous system certainly does not mean true diabetes. The literature in recent years has not yielded any conclusive case reports. Incidentally, the polydipsia and polyuria without glycosuria of diabetes insipidus have sometimes been thought to be due to syphilitic involvement. In our own cases of diabetes with syphilis we have had no cases of diabetes insipidus, though the two diseases have been known to occur together, there having been at least 2 cases of nonsyphilitic coexistent diabetes insipidus and diabetes mellitus in the whole diabetic practice.

Endocrine Glands—Labbé and Touffet² mentioned that in some cases diabetes is found in association with endocrine disturbances, such as exophthalmic goiter, acromegaly and possibly some adrenal dysfunctions. They believed that if such combinations occurred and were due to syphilis of the endocrine glands, then there would be a new category of syphilitic diabetes. They had never seen such a condition.

Autopsy Reports—Warren,¹⁴ in his series of 486 autopsies on persons with diabetes (the largest series in the literature and chiefly taken from our practice), did not find a single pancreas in which he felt syphilis was responsible for the diabetes. Occurrence of syphilitic lesions in other organs was rare. There were only 2 diabetic patients dying as a result of syphilis. In 1 with diabetes of three years' duration, there was a syphilitic tracheal ulcer, and in the other with diabetes of

13 Labbé and Touffet² Lemann³ Rosenbloom⁴

14 Warren, S. *The Pathology of Diabetes Mellitus*, ed. 2. Philadelphia: Lea & Febiger, 1938.

three months' duration, an abdominal aneurysm had ruptured. He felt that his diabetic material was apparently different from that of Warthin.

Simmonds¹⁵ was cited by Lemann⁸ as doing 300 autopsies on diabetic patients.

Changes in the pancreas of a nonsyphilitic nature were apparent in about 90 per cent. Two cases of gumma of the pancreas were found and one died of myocarditis gummosa and one of tabes. In three diabetics with syphilis the pancreas was small, weighing 26 to 36 grams and was adherent to the surrounding tissues being of fibrous structure in which bean-sized remnants of gland tissue were recognized. He considered the fibrotic atrophy to be a result of preceding syphilis. In the 300 cases, syphilis was found in only 20 instances. In 17 of these there was no evidence that the syphilis and diabetes were dependent one on the other.

Seyfarth¹⁶ was also cited by Lemann as having performed 289 autopsies on diabetic patients. In only 26 were there syphilitic changes in the organs.

CASES IN THE LITERATURE

Certain reviews¹³ have given case reports in great numbers. The facts concerning the majority of them have been so meager that reviewing them is not worth while. All too often the diagnosis of syphilis is a difficult one to make, and it was even more so before 1907 and the introduction of the Wassermann test. Similarly, with patients with glycosuria comparatively little was known about the disorder until the general introduction of blood sugar analyses about twenty-five years ago. A further significant point is that the whole picture of diabetes was changed when the use of insulin was generally adopted about 1923, when important changes were made in dietary schemes. Practically no case in the literature would satisfy Troller's postulates or withstand very critical judgment. To conserve space, our review of the literature in recent years, both American and foreign, has been omitted except for a few important cases.

Paullin and Bowcock¹⁷ reported an unusual case with significant results of dextrose tolerance tests.

The case is that of a single 21 year old woman with a positive Wassermann reaction and a normal history, the syphilis supposed to be of congenital origin. There was 11 per cent of glycosuria and diacetic acid on the first visit. Antisyphilitic therapy was carried out almost

15 Simmonds, M. Diabetes and Syphilis, *Arch f Dermat u Syph* **132** 235, 1921.

16 Seyfarth, C. Neue Beitrage zur Kenntnis der Langerhanschen Inseln im menschlichen Pankreas und ihrer Beziehung zum Diabetes mellitus, Jena, Gustav Fischer, 1920.

17 Paullin, J. E., and Bowcock, H. M. Treatment of Syphilis Coexistent with a Condition Simulating Diabetes, *J. A. M. A.* **82** 702-705 (Nov 1) 1924.

steadily for about two years. Gradually, the dextrose tolerance test approached normal, and she was able to take a general diet without glycosuria. The determinations of fasting blood sugar gave normal results. The Wassermann reaction remained positive. Even the original abnormal curves were not typical of diabetes, since the rise of the level of blood sugar in the first two hours was not sustained as in true diabetes, the authors did not state, however, that the patient had true diabetes.

Elmer and Kedzierski,¹⁸ in an excellent paper, brought out several new thoughts. In 1 of their cases glycosuria disappeared and the blood values returned to normal after antisyphilitic treatment but a dextrose tolerance test showed diabetes still to be present. A second of their cases practically fulfils all the criteria for cure. In this case antisyphilitic treatment caused disappearance of glycosuria, reduction of blood sugar to normal levels and restoration of normal dextrose tolerance. So far

TABLE 1—*Dextrose Tolerance Tests in a Diabetic Patient Before and After Antisyphilitic Treatment **

Time, Minutes	Sugar April 1921		Sugar January 1923		Sugar July 1923	
	Urine, Gm	Blood, per Cent	Urine, Gm	Blood, per Cent	Urine, Gm	Blood, per Cent
0	0	0.14	0	0.08	0	0.10
30	2.0	0.32	0.5	0.28	++	0.17
60	3.5	0.42	1.5	0.20	++	0.17
90	2.5	0.28	0.5	0.18	0	0.16
120	0	0.19	0	0.06	0	0.10

* The case was reported by Paullin and Bowcock.¹⁷

† The greatest amount excreted was 0.35 Gm.

as they knew this was the first case in the literature conforming to such standards. However, at the end of the first half-hour in the dextrose tolerance test the blood sugar content was 185 mg per hundred cubic centimeters, which is higher than our critical level of 170 mg per hundred cubic centimeters. They recognized this slightly extra high elevation and pointed out that at the end of one hour the blood sugar level went below normal, a process which would not occur in a diabetic patient. Therefore, they were perhaps justified in concluding that they were not dealing with a diabetic patient with syphilis but with a syphilitic patient with diabetes. In their comments they pointed out the fallacy that many authors start out with the belief that nonsyphilitic diabetes is never cured and therefore that any diabetic patient who is cured is syphilitic.

18 Elmer, A. W., and Kedzierski, J. Valeur du traitement spécifique dans le diagnostic du diabète syphilitique, *Ann de med* 24 332-339 (Oct.) 1928.

Kitchell⁹ reported on "50 patients with a positive blood Wassermann reaction and undoubted diabetes as shown by both blood and urine studies" Thirty-one of these patients had no antisyphilitic therapy or an obviously inadequate amount of medication for any therapeutic effect to be expected A second group, of 15 patients, received adequate (no details given) antisyphilitic therapy, but with no effect on the diabetic condition A third group, of 4 patients, reported on in detail, were those whose diabetic symptoms disappeared under antisyphilitic treatment We can find nothing conclusive regarding these 4 patients, there being many unfulfilled criteria and criticisms Kitchell concluded that "the recovery of patients with syphilitic diabetes after antisyphilitic treatment was more apparent than real, and the eventual relapse into the diabetic state was probably the fate of all of them" Of course he probably had an idea that there was not such a thing as syphilitic diabetes At least he knew that in his cases cures had not been effected

SPECIFICITY OF SEROLOGIC TESTS

At this point comment should be made on the specificity of serologic tests in diabetic patients In the early days of serologic testing much experimentation was going on with the Wassermann test Richards¹⁹ reported 4 cases of diabetic acidosis in which the patients had positive Wassermann reactions, and in none of these were the patients supposed to have had syphilis Richards' belief that in some way diacetic and betaoxybutyric acids may cause false positive reactions has never been borne out In checking such a possibility, Walker and Haller²⁰ found that in a group of 89 cases of diabetes, in which 7 patients had positive Wassermann reactions and the majority gave a history of syphilitic infection, repeated tests under various conditions showed the Wassermann reaction was not influenced whether there was much or little sugar in the blood or in the urine and whether or not the patient was in coma Van Saun²¹ reported results in 73 cases of known diabetes Most of the serums were chylous The serum of only a single patient gave a positive reaction, and this patient had a history of syphilis In 19 cases the serum controls failed to hemolyze, so that readings could not be made Van Saun stated that nonspecific reactions given by 19 serums in this series might easily have been supposed to be positive

19 Richards, J H The Wassermann Reaction in Diabetes Mellitus with Special Reference to Its Relation with Acidosis, *J A M A* **60** 1139-1141 (April 12) 1913

20 Walker, I C, and Haller, D A Routine Wassermann Examinations of Four Thousand Hospital Patients, *J A M A* **66** 488-491 (Feb 12) 1916

21 Van Saun, A I Wassermann Reaction with Diabetic Sera, *J M Research* **37** 205-206 (Nov) 1917

had not their anticomplementary qualities been fully demonstrated by the double as well as by the single serum controls. She concluded that with carefully controlled tests nonspecific fixations can always be checked. Williams²² in 143 cases of diabetes had 4 positive Wassermann reactions. The serum in only 1 of these cases had abnormal amounts of cholesterol. In 37 of the cases there was cholesteremia the content of cholesterol being more than 250 mg per hundred cubic centimeters, and in these cases the reactions were negative. Since the presence of cholesterol increased the delicacy of the test, the author thought that if any of these patients had the slightest trace of syphilitic infection they would have reacted positively to the Wassermann test. We might add that blood cholesterol values in diabetic patients were higher before the general adoption of insulin and of the feeding of diets less high in fat, in 1923. Mason²³ cited 2 cases in which he attributed positive Wassermann reactions to a disturbed physicochemical relationship. In each case the reaction became negative after two arsenical treatments. Close observation of the simultaneous dates of the tests would suggest some error in the laboratory. Root and Stuart,²⁴ on our own series of diabetic patients, studied the effects of variations in the levels of sugar and cholesterol in the blood and the effects of acidosis and of albuminuria on the reactions to 1,078 Wassermann, Hinton and Kahn tests, without finding evidence of any false reactions. Richardson²⁵ found that certain human serums specifically fixed complement in the presence of regular insulin as supplied to the patient. In a study of a number of diabetic patients of all sorts the Wassermann reaction was negative in every case, so he found no definite correlation between the clinical condition and the reaction. In no serum were the Wassermann and insulin reactions both positive.

To sum up the subject of specificity, we find no evidence of false positive serologic reactions due to the abnormalities observed in diabetes mellitus. In our own series of diabetic patients the cholesterol contents of the blood have been frequently determined, usually as a check for diabetic control. Of the 258 diabetic patients with syphilis the cholesterol contents happened to be determined in 36 patients. In not a single one of these was there any relation to the specificity of the test. Of the

22 Williams, J. R. Syphilis as a Cause of Diabetes Mellitus. Relation of Wassermann Test and of Lipoidemia, *J. A. M. A.* **70**:365-367 (Feb. 9) 1918.

23 Mason, E. H. Non-Specific Wassermann Reactions in Diabetes Mellitus, *Am. J. M. Sc.* **162**:828-833 (Dec.) 1921.

24 Root, H. F., and Stuart, G. O. Hinton, Kahn and Wassermann Reactions in Diabetes, *New England J. Med.* **204**:1179-1181 (June 4) 1931.

25 Richardson, R. Complement Fixation with Insulin as Antigen, *Proc. Soc. Exper. Biol. & Med.* **38**:874-875, 1938.

36 patients, 23 had normal cholesterol values. Of the remaining 13 patients with blood cholesterol values elevated to a greater or lesser degree, 7 gave a history of syphilitic infection, and the remaining 6 patients, for whom there was no history of syphilis, had serologic reactions that remained persistently positive and a history of sterility or of miscarriages. In our cases we have found that the blood dextrose value, whether high or low, has no effect on serologic reactions.

CRITERIA FOR DIAGNOSES AND METHODS

Our series of cases have fulfilled certain easily defined criteria.

Diagnosis of Diabetes—A diagnosis of diabetes has been made if the patient had glycosuria and if the venous blood sugar content was 0.14 per cent while the patient was fasting or 0.17 per cent at any other time in the day. When the capillary blood sugar content was determined, the fasting value was considered the same, but the other value was raised to 0.20 per cent.²⁶

Diagnosis of Syphilis—A diagnosis of syphilis has been made in practically all cases when there was a positive reaction to a serologic test of the blood by the technic of Hinton, Kahn or Wassermann, in addition to which in many cases there was a history of syphilitic infection with or without treatment, and, in some cases, the presentation of syphilitic manifestations as seen grossly or by pathologic section. In most cases in which positive reactions were obtained, the tests have been repeated, in different laboratories. Since April 1934 the routine serologic test has been the Hinton test.²⁷ In the entire series of 17,500 patients with glycosuria, of whom 15,095 are patients with true diabetes, a routine serologic test has been done on the first visit for almost the entire number, the exceptions being those patients who were seen in the years prior to the discovery of the serologic tests. After case 6 of syphilis with glycosuria, first encountered in 1910, in all the cases of syphilis serologic tests have been performed. Of the entire series of 17,500 cases there are 42 cases in which a positive serologic reaction has not been confirmed by repeat tests, by history or by physical examination, and in addition, there were many others in whom the initial

26 (a) Joslin, E. P., Root, H. F., White, P., and Marble, A. *The Treatment of Diabetes Mellitus*, ed. 6, Philadelphia, Lea & Febiger, 1937. (b) Smith, M. A. Micro Modification of the Method of Benedict for the Quantitative Determination of Reducing Sugar in the Urine, *J. Lab. & Clin. Med.* **7**: 364-368 (March) 1932. (c) Folin, O. *Laboratory Manual of Biological Chemistry*, ed. 5, New York, D. Appleton-Century Company, Inc., 1934. (d) The Micro Method for the Determination of Blood Sugar, *New England J. Med.* **206**: 727-729 (April 7) 1932.

27 Hinton, W. A., and Davies, J. A. V. The Hinton and Davies-Hinton Tests for Syphilis, *Ven. Dis. Inform.*, 1939, supp. 9, pp. 172-182.

serologic test was reported as "doubtful" and subsequently was not confirmed. In none of these cases are the patients considered to be syphilitic, and they are disregarded in this paper. There are some cases in our series of 258 in which there was a single positive reaction to the serologic test but in which there was no reason for doubting the diagnosis.

Cure of Diabetes—Most of the cases of syphilis and diabetes reported in the literature speak of cure of the diabetes after antisyphilitic treatment but give no details or do not confirm to standards of cure. As we see the situation, the proof of cure is the most important aspect of the problem to those who would say that syphilis might cause diabetes. For so many of the so-called cures reported in the literature, a dextrose tolerance curve would show cure not to be complete. The criteria for cure have been well stated by Root and Marble,²⁸ and their statements are summarized as follows:

Diagnosis Same as previously stated.

Duration of Proved Diabetes The duration of proved diabetes, by repetition of the tests described under diagnosis, shall be recorded in months. The longer the duration of the proved diabetes, the greater the importance which will be attached to its cure. Chance glycosuria and hyperglycemias resulting from errors in the laboratory, from operative procedures and from temporary infections are thus ruled out.

Test for Recovery Glycosuria and hyperglycemia shall be absent while the patient is without diabetic medication, both before and an hour after a meal. This meal must contain at least two-fifths of the carbohydrate for the day. The carbohydrate for the 24 hours shall comprise at least two-thirds of the calories necessary to provide 30 calories per kilogram of body weight. Better still, the carbohydrate tolerance shall be unimpaired as judged by a normal glycemic curve following the oral administration of 50 to 100 grams of glucose to the patient in the post-absorptive state.

Establishment of Recovery A proved case of one or more months' duration, which conforms to the test for recovery at the beginning and end of an interval of five or more years, shall be considered.

Diagnosis of Coma—Cases of diabetic acidosis have been classified arbitrarily as being cases of diabetic coma when the carbon dioxide-combining power of the blood plasma was found to be 20 volumes per cent or below, whether or not the patient was comatose.²⁹

Classification of Severity of Diabetes—Classification such as that which follows is purely arbitrary, and the insulin requirements if any

28 Root, H. F., and Marble, A. Progress in Diabetes Mellitus. New England J. Med. **218**: 918-933 (June 2) 1938.

29 Van Slyke, D. D. A Method for the Determination of Carbon Dioxide and Carbonates in Solution. I. Biol. Chem. **30**: 347-365, 1917. Van Slyke, D. D. and Stadie, W. C. The Determination of the Gases of the Blood, *ibid.* **49**: 1-42 (Nov.) 1921.

are taken under ordinary conditions of control, when the patient is not suffering from pyogenic infection or any other complicating condition, except possibly syphilis

Mild diabetes	20 or below	} Daily insulin dose in units
Moderate diabetes	20 to 40	
Severe diabetes	40 or above	

Degree of Control of Diabetes—A diabetic patient may be said to be under good control if while on a well proportioned diet, with or without insulin, he is maintained in a state of good nutrition with reasonable activity and if the content of sugar in the blood or in the urine is not above 10 per cent of the carbohydrate intake per twenty-four hours, if the blood sugar values are below 200 mg per hundred cubic centimeters, and if the blood cholesterol content does not rise above 230 mg per hundred cubic centimeters

Blood Cholesterol—These values were determined by the technic of Bloor³⁰

Hypertension—A patient was classified as having hypertension if the blood pressure at rest exceeded the following limits at the age of 30 or less, 145 systolic and 90 diastolic, and above 30, 150 systolic and 95 diastolic

Optimal Antisyphilitic Treatment—In describing the "cure" for syphilis it is improper to state that a certain amount of treatment is adequate, and "optimum" is the better term to apply to a subject so controversial in nature. We have in general considered our patients to have had satisfactory treatment if they have received a certain amount of treatment as outlined by the Cooperative Clinical Group working in association with the United States Public Health Service. In brief, in the treatment of early syphilis³¹ the patient should from the very start receive continuous alternating courses of an arsphenamine and a bismuth compound, receiving not less than twenty and usually not more than thirty injections of the arsphenamine. The patient should also receive uninterrupted treatment with a heavy metal in the second year, or longer if necessary, until all symptoms and signs of the disease have dis-

30 Bloor, W R. The Determination of Small Amounts of Lipid in Blood Plasma, *J Biol Chem* **77** 53-73 (April) 1928

31 Stokes, J H, Cole, H N, Moore, J E, O'Leary, P A, Wile, U J, Parran, T, Vonderlehr, R A, and Usilton, L J. The Standard Treatment Procedure in Early Syphilis, *J A M A* **102** 1267-1272 (April 21) 1934. Moore, J E, Cole, H N, Schamberg, J F, Solomon, H C, Wile, U J, and Stokes, J H. Management of Syphilis in General Practice, *Ven Dis Inform* **10** 53-89 (Feb 20) 1929. Stokes⁵

appeared. In cases of latent or late syphilis,³² in which the patient cannot be treated by such a routine method and with such intensiveness because the condition may demand modifications, he ordinarily should receive ten weekly injections of an arsphenamine followed by ten weekly injections of a bismuth compound, the courses being alternated until there have been a total of thirty injections of each. An iodide is given the first year along with the bismuth preparation and in the second year between the bismuth courses, during which year the patient is given three courses of ten weekly bismuth injections, a rest period of ten weeks being allowed between each course. Inunctions of strong mercurial ointment may be substituted for bismuth in the second year.

STATISTICS

In the diabetic practice from which we report, a list has been continuously kept of those patients with glycosuria whose reactions to routine serologic tests turned out to be positive and also of those patients whose reactions were negative but who gave a history of syphilitic infection with treatment. The great majority (86 per cent) of the patients with glycosuria have satisfied the criteria of true diabetes mellitus, but there are some with unclassified glycosuria, with renal glycosuria and with deferred diagnoses. This study concerns itself only with cases of true diabetes with syphilis. Our cases include 5 in which the condition was originally considered either as potential diabetes (3) or as unclassified glycosuria (2), and a study of them does not cast any suspicion on syphilis as being the agent responsible for the increase in hyperglycemia necessitating a change of the classification to true diabetes. The series of cases of glycosuria began in 1897, with the first 1,000 cases of diabetes observed by 1916, 3,000 by 1923 and the rest in increasing proportions since that date. The records in the cases of syphilis have been closely scrutinized, with many items arranged for statistical analysis. The first syphilitic patient was seen in 1902. The last patient whose record was used was the two hundred and fifty-eighth syphilitic patient, with case number 17,500, and this series ended Dec 31, 1938. As far as possible the surviving diabetic patients with syphilis in this series were traced to 1938, and many to March 1939.

Incidence—The incidence of syphilis among the diabetic patients in each group of 1,000 patients is seen in table 2.

Thus it is observed that of 15,095 diabetic patients there have been 258 with syphilis, an incidence of 1.7 per cent. Table 3 combines our

32 McLester, J. S. in Cecil, R. L. *A Textbook of Medicine* ed. 4 Philadelphia, W. B. Saunders Company, 1937. Cole, H. N. *The Use of Arsenoplatin Remedies*, I. A. M. A. **107** 2123-2131 (Dec. 26) 1936. Moore.

statistics with some found in the literature and some drawn from tables presented by Labbé and Touffet ² and Lemann ³ We wish to point out that our incidence of 17 per cent comes from the largest group of

TABLE 2—*Incidence of Syphilis Among Diabetic Patients in Each Thousand Patients **

Case Number	Patients With Diabetes Mellitus	Diabetic Patients With Syphilis	Per Cent
0 - 1,000	911	20	2.2
1,001 - 2,000	875	16	1.8
2,001 - 3,000	867	19	2.2
3,001 - 4,000	857	26	3.0
4,001 - 5,000	831	21	2.5
5,001 - 6,000	840	13	1.5
6,001 - 7,000	860	15	1.7
7,001 - 8,000	845	11	1.3
8,001 - 9,000	826	10	1.2
9,001 - 10,000	876	6	0.7
10,001 - 11,000	892	14	1.6
11,001 - 12,000	853	10	1.2
12,001 - 13,000	831	13	1.6
13,001 - 14,000	842	11	1.3
14,001 - 15,000	887	13	1.5
15,001 - 16,000	925	17	1.8
16,001 - 17,000	843	15	1.8
17,001 - 17,500	434	8	1.8
Total	15,095	258	1.7

* Unless otherwise designated, data in the following tables are obtained from the experience of E. P. Joslin and associates, 1897-1939.

TABLE 3—*Syphilis in Diabetes*

Author	Diabetic Patients Examined	Diabetic Patients with Syphilis	Percentage
Joslin *	15,095	258	1.7
Williams ²²	143	4	2.8
Walker and Haller ²⁰	89	7	7.9
Stott, H. Indian M. Gaz. 65 196 197 (April) 1930	100	Under 25 years old	50.0
Rosenbloom ⁴	139	Over 25 years old	32.0
Curschmann ³⁰		16	11.5
Labbé and Touffet ²	500	17	4.3
		39 certain	7.8
		28 doubtful	5.6
Schmidt ²	2,500	12	0.5
Frerichs ²	400	4	1.0
Teschemacher ²	1,231	2	0.16
Joblotskoff ²	79	5	6.3
Weil ²	14	1	7.1
Verdalle ²	129	8	6.2
Hirschfeld ²			6.0
Gallus (1920) ³	609	49	8.0
von Noorden ³		Male, under 20	1.2
		Male, over 20	7.1
		Female, all ages	2.3
John ³	2,000	54	2.7
Mason ³	168	2	1.2
Lemann ⁴³	471	14	2.9

* Data from the experience of E. P. Joslin in 1939.

diabetic patients whose diagnoses have met rigid criteria. Furthermore, many of our patients have been seen over an extended period of time and do not merely represent a cross section taken at a particular moment.

Labbé and Toufflet² tried statistical methods to find a relationship between syphilis and diabetes. Investigation for syphilis in a group of diabetic and a group of nondiabetic patients was carried out, and the percentage of syphilis in the former was not significantly different from the percentage in the latter. They did not study a group of syphilitic patients to see how many had glycosuria, but in reviewing the work of others on this problem they found no evidence that syphilis played an important etiologic role in diabetes.

The incidence of syphilis in our diabetic patients (17 per cent) should be compared with the incidence of syphilis in the general population of this locality. Such data are hard to obtain because the only data that would be comparable would be those of a rather old population of about the same age. Merritt and Moore³³ reported an average incidence of 2.26 per cent for a ten year period in the largest hospital in Boston. This value was an absolute minimum, because there is no syphilis clinic at that hospital, because routine serologic tests were not made on all patients and because the character of the patients coming to that hospital would lead one to expect a larger percentage. It is definite that in this region of the country syphilis is not more common in diabetic than in nondiabetic patients.

Sex—Of the 258 diabetic patients with syphilis, there were 188 males and 70 females, a ratio of only 37.2 female to each 100 male patients. This is in great contrast to the ratio in whole series of diabetic patients from 1897 to 1933, in which there were 112.4 female per 100 male patients. When the entire diabetic practice is considered, 2.7 per cent of the male and 0.9 per cent of the female patients were syphilitic. This difference is a good point in the proof that syphilis has little to do with diabetes, because the ratio of male to female diabetic patients with syphilis corresponds to that of syphilitic patients as a group and is so definitely not in agreement with the ratio of male to female diabetic patients as a group, in most series of whom the number of female patients exceeds that of male patients.³⁴

Means of Identification—The method of identification used in separating the syphilitic from the diabetic patients as a whole is easily seen in table 4. The elimination of many cases has been described in a preceding paragraph. From the table it is evident that 51.6 per cent of the cases were identified by serologic tests alone. In accordance with the fact that syphilitic infection is less frequently found in the early stages in women as compared with men it is obvious that our statistics

33 Merritt, H. H., and Moore, M. The Problem of Syphilis in the Wards of a Large General Hospital. *New England J. Med.* **219**: 834-835 (Nov. 24) 1937.

34 Joslin, E. P., Dublin, L. I., and Marks, H. H. Studies in Diabetes Mellitus. IV. Etiology, *Am. J. M. Sc.* **192**: 9 (July) 1936.

agree, only 86 per cent of the women having knowledge of the initial infection, as compared with 213 per cent of the men. The 178 per cent identified by history alone chiefly represent those cases with a history of syphilitic infection that had been treated, so that by the time the patients reached our office the routine serologic tests gave negative results. Serologic tests were done in 97.7 per cent of the 258 cases.

Stage of Syphilis at First Observation—As would be expected, according to table 5 it is seen that at the time of the first examination, in 86.8 per cent of all cases the patients have reached the latent stage.

TABLE 4—*Means of Identifying Syphilis Among Diabetic Patients with Syphilis*

	Per Cent			Number		
	Total	Male	Female	Total	Male	Female
Total	100.0	100.0	100.0	258	188	70
Serologic test only	51.6	43.1	74.3	133	81	52
History only	17.8	21.3	8.6	46	40	6
Physical signs	0.8	0.5	1.4	2	1	1
Serologic test and history	18.6	21.3	11.4	48	40	8
Serologic test and physical signs	8.1	9.6	4.3	21	18	3
History and physical signs	1.6	2.1		4	4	
Serologic test, history and physical signs	1.2	1.6		3	3	
Unknown	0.4	0.5		1	1	

TABLE 5—*Stage of Syphilis at Time of First Examination of Diabetic Patients With Syphilis*

	Per Cent			Number		
	Total	Male	Female	Total	Male	Female
Total	100.0	100.0	100.0	258	188	70
Latent	86.8	86.7	87.1	224	163	61
Primary stage						
Secondary stage	1.2	1.6		3	3	
Tertiary stage	8.5	9.0	7.1	22	17	5
Not stated	3.5	2.7	5.7	9	5	4*

* Includes 1 case in which there was a question as to whether the disease was in the second or the tertiary stage.

of syphilis. Diabetes is generally a disease that manifests itself in or after middle age, and this is the time that a syphilitic infection, usually acquired in earlier life, has had time to reach the so-called latent stage. In no cases was syphilis observed in the primary stage. Of course if one were to consider diabetes as being produced by syphilis, in the majority of the cases of latent syphilis the disease would be judged as being in its tertiary stage, with diabetes a syphilitic manifestation. The cases of syphilis in the tertiary stage, as listed in table 5, are those with gummas, syphilis of the central nervous system or syphilis of the cardiovascular system.

Residence—A table to give in detail the residence of these diabetic patients with syphilis is not necessary. Of all the patients there were 70.9 per cent from Massachusetts and 44.2 per cent were from the local area of metropolitan Boston. Fourteen per cent were from the other New England states, 8.2 per cent came from New York, New Jersey and Pennsylvania, and the others were from other states and countries.

Nationality or Race—The race of the patient has little bearing apparently on the relationship between the two diseases, but there are two items worth noting. Table 6 compares the race or nationality of the diabetic patients with syphilis in our series with a very large number of diabetic patients in the same practice. Only the more commonly observed races are included. In those races with enough cases to be statistically important there is no essential difference, except in the

TABLE 6—*Nationality or Race of Diabetic Patients With Syphilis, 1897-1939*
*Comparison by Sex With All Diabetic Patients Observed, 1897-1928**

Nationality or Race	All Syphilitic Patients	Male		Female	
		Syphilitic Patients Only	All Diabetic Patients*	Syphilitic Patients Only	All Diabetic Patients*
Number of cases	258	168	2,770	70	2,914
Known nationality	249	181	2,411	68	2,617
American	63.2	64.9	65.9	58.6	59.1
Jewish	7.8	7.4	14.2	8.6	18.9
Scotch	2.7	2.1	1.0	4.3	1.1
Canadian	6.2	5.3	5.7	8.6	5.2
Italian	3.9	3.7	1.7	4.3	2.1
Irish	3.1	3.2	3.0	2.9	5.1
German	1.2	1.1	0.5	1.4	1.1
Swedish	1.2	1.6	1.1		0.8
Negro	1.9	1.1	0.2	4.3	0.4

* Statistics from Joslin, Dublin and Marks. *Am J M Sc* 1929 (July) 196.

Jewish race and in Negroes. In this practice, at least, there is definitely less syphilis in the Jewish patients, yet in comparison with the other races diabetes is definitely found more frequently in Jews, the proportion of Jewish patients being far in excess of their proportion in the population in this area (8 per cent)³⁴. As regards Negroes, there were only 2 male and 3 female patients in the whole series of syphilitic patients, but even in this small group it is noteworthy that there is a higher proportion of Negro diabetic patients with syphilis than in white patients. We do not believe this indicates any relationship between diabetes and syphilis, because the Negro race is known to be heavily afflicted with syphilis. Lemann³⁵ working with data from a hospital with a large number of Negro patients, was convinced there was no relation between the incidence of diabetes and that of syphilis. Of the

35 Lemann I I. Diabetes Mellitus Syphilis and the Negro, *Am J M Sc* 1921 226-230 (Aug) 1921.

large number of patients admitted to the hospital, Negroes comprised 40 per cent of the total admitted and 30 per cent of the number of diabetic patients, though they furnished over 50 per cent of the number with syphilis

Marital State—The marital status is briefly described in table 7, without any attempt to indicate distinctions of age

Fertility—Investigation of this aspect of the coexistent diseases proves interesting One is impressed by the number of childless marriages when either of the marriage partners is afflicted with the two diseases The situation is shown in table 8, and several reasons

TABLE 7—*Marital Condition by Sex of Adult Diabetic Patients with Syphilis Aged Twenty and Over at Time of First Visit*

	Male		Female	
	Per Cent	Number	Per Cent	Number
All cases	100 0	186	100 0	69
Single	14 5	27	8 7	6
Married	76 9	143	55 0	38
Widowed	5 9	11	27 6	19
Divorced, separated	2 7	5	8 7	6

TABLE 8—*Fertility of Married Adult Diabetic Patients With Syphilis Aged Twenty and Over at Time of First Visit*

	Per Cent			Number		
	Total	Male	Female	Total	Male	Female
Total, all married patients				222	159	63
Total, no children or pregnancies	32 4	30 2	38 1	72	48	24
No children or pregnancies	25 7	27 0	22 2	57	43	14
All stillbirths, miscarriages or died in infancy	4 5	1 9	11 1	10	3	7
One or two living children and many miscarriages or stillbirths	2 3	1 3	4 8	5	2	3
Not stated or unknown	3 2	4 4		7	7	

account for it Syphilis has long been known either to cause sterility or to produce miscarriages or defective children that soon die Diabetes, for its share, produces two effects In the first place, patients with diabetes are usually older people who are naturally less likely to reproduce, even if they are still in the childbearing age, and, in the second place, because of the diabetes itself the patient is less fertile—though this is less true than formerly, in these days of good control of diabetes with insulin Not to be overlooked in diabetic male patients is the frequent complaint of impotence, a symptom which is usually not inquired about In our experience there have been no pregnant diabetic women with syphilis

Presence of Gonorrheal Infection—Gonorrhea and syphilis are not uncommonly contracted simultaneously. Much stress has not been laid on questioning the patients at the time of the first visit concerning a history of gonorrheal infection. Table 9 gives the information that was obtained and naturally represents the very minimum of infection.

TABLE 9—Incidence of Gonorrhea Among Diabetic Patients With Syphilis

	Per Cent		
	Total	Male	Female
Total	100.0	100.0	100.0
Positive	15.0	20.7	2.9
Denied	10.1	12.8	2.9
Not stated (not questioned)	71.3	63.3	92.9
Unknown	2.3	2.7	1.4
Doubtful	0.4	0.5	

TABLE 10—Ages at Onset of Diabetes in Diabetic Patients With Syphilis and of All Diabetic Patients*

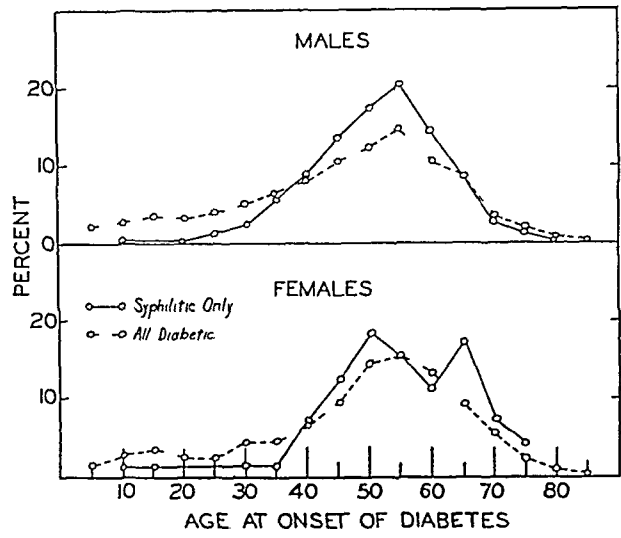
Ages	Male				Female			
	Per Cent		Number		Per Cent		Number	
	Syphilitic Diabetic Patients	All Diabetic Patients †	Syphilitic Diabetic Patients	All Diabetic Patients	Syphilitic Diabetic Patients	All Diabetic Patients †	Syphilitic Diabetic Patients	All Diabetic Patients
All ages	100.0		183	3,124	100.0		70	2,271
Under 5		2.1		66		1.6		51
5 - 9	0.5	2.9	1	90	1.4	2.9	1	91
10 - 14		3.8		118	1.4	3.5	1	112
15 - 19	0.5	3.3	1	102		2.6		85
20 - 24	1.6	4.0	3	125		2.4		77
25 - 29	2.7	5.3	6	164	1.4	4.2	1	144
30 - 34	5.0	6.6	11	205	1.4	4.4	1	142
35 - 39	8.5	8.1	16	254	7.1	6.8	5	210
40 - 44	13.8	10.3	26	322	12.0	9.7	9	144
45 - 49	17.6	12.7	33	397	18.6	14.0	11	144
50 - 54	20.2	14.4	38	451	15.7	13.7	11	207
55 - 59	14.4	10.7	27	376	11.4	11.6	8	411
60 - 64	8.5	8.7	16	271	17.1	9.2	12	207
65 - 69	2.7	3.8	5	118	7.1	5.8	5	187
70 - 74	1.6	2.2	3	68	4.3	2.1		107
75 - 79	0.5	0.9	1	27		1.0		27
80 - 84		0.2		5		0.2		5
Unknown	1.1		2	5				4
Median age			49.0	46.7			51.0	47.2

* Taken from table 10, P. Joslin, *Treatment of Diabetes Mellitus and Its Complications*, Lea & Febiger, 1927, data compiled by the Statistical Bureau of the Metropolitan Life Insurance Company.

† Based on total of known age.

Age of Onset of Diabetes in Diabetic Patients with Syphilis—Concerning the time of onset of diabetes our records are as accurate as it is possible for them to be, since great stress has been made on this point since the very beginning of the series. In table 10 are compiled the data for the series of 258 diabetic patients with syphilis and these are compared with similar data of a series of 6,357 diabetic patients. The median age for the onset of diabetes in male diabetic patients with

syphilis is 49 0 years, as compared with 46 5 years in the entire series of diabetic patients The seemingly earliest onset in these patients in the first thirty-five years is explained by the fact that this series contained over 1,400 children and there were only 3 children among the



Percentages by sex of diabetic patients with syphilis and all diabetic patients having onset of diabetes in specified age periods These curves have been prepared from data given in table 10

TABLE 11—Age at Onset of Syphilis in Diabetic Patients With Syphilis (in Only Those Cases in Which Time of Onset Was Known), Comparison of Diabetic Male with Nondiabetic Male Patients

Age at Onset	Number			Per Cent *		Massachusetts Male † Patients per Cent 1930 1937
	Total	Male	Female	Total	Male	
All ages	77	71	6	100 0	100 0	
0 14	3	1 ‡	2 ‡	3 9	1 4	0 3
15-19	12	11	1	15 6	15 5	3 8
20 24	19	19		24 7	26 8	21 2
25 29	16	15	1	20 8	21 1	22 9
30 34	11	10	1	14 3	14 1	16 6
35 39	6	5	1	7 8	7 0	13 3
40 49	8	8		10 4	10 4	14 1
50 plus	2	2		2 6	2 6	7 9
Mean	27	28	20			
Median	26	27	20			

* Per cent for female patients not calculated because small number with known onset would not give significant values
† Data from reports of 6,168 male diabetic patients with cases of early (primary and secondary) syphilis in Massachusetts from 1930 through 1937 ³⁶
‡ Diabetic patients under 5 years of age with congenital syphilis

diabetic patients with syphilis The information from this table is graphically shown in the chart It is thus observed that the age at onset of diabetes is the same for patients with or without syphilis The curves of onset are the same for the two sexes We consider this to be a very important point, and nothing in the literature previously has referred to it

Age at Onset of Syphilis in Diabetic Patients with Syphilis—To determine the age at which the onset of syphilis occurs is much more difficult than to determine the age at which the onset of diabetes occurs. In so many persons, especially in women, the time of the initial infection is never known, the presence of syphilis being later detected by a

TABLE 12—*Maximum Weight by Sex Prior to First Visit of Adult Diabetic Patients with Syphilis (1897-1939) Compared With Maximum Weight of Diabetic Patients* (1898-1928), Also Weight at First Visit of Adult Diabetic Patients With Syphilis (Both Sexes), Percentage in Groups Classified by Deviation from Average Weight for Height and Age*

Weight Group	Previous Maximum Weight					Weight at First Visit Adult Syphilitic Patients Both Sexes
	Male		Female		Both Sexes	
	Syphilitic Patients Only	All Patients *	Syphilitic Patients Only	All Patients *		
All cases	100 0	100 0	100 0	100 0	100 0	100 0
Overweight, total (5% or more above average)	81.2	78.5	87.9	83.7	83.1	72.6
20% or more	55.7	51.0	72.7	59.3	69.4	15.9
40% or more	20.2	16.5	37.9	25.8	25.1	7.1
30% to 39%	16.0	13.9	17.2	14.2	16.4	6.1
20% to 29%	19.5	20.6	17.2	19.3	18.8	6.7
5% to 19%	25.5	27.5	15.5	24.0	22.7	17.7
Normal weight (less than 5% above or below average)	13.4	13.6	6.9	10.4	11.6	19.0
Underweight, total (5% or more below average)	5.4	7.9	5.2	6.3	5.7	47.7
5% to 19%	4.7	7.1	1.5	5.5	4.1	28.8
20% or more	0.7	0.8	1.7	0.8	1.0	19.0
Number of cases	119 †	2,251	58	2,745	207 †	2,641

* Data from table 27, L. P. Joslin *Treatment of Diabetes Mellitus*, ed. 6 Philadelphia, Lea & Febiger, 1937.

† Number of cases with this information available from 258 cases of diabetes compiled from data prepared by the statistical bureau of the Metropolitan Life Insurance Company.

TABLE 13—*Priority of Syphilis Among Diabetic Patients With Syphilis*

	Total	Male	Female
Both sexes	258	188	70
Number of known cases	107 (41.5%)	91 (47.8%)	17 (24.3%)
Number of "probable" cases	112 (43.4%)	71 (37.8%)	41 (58.6%)
Time relationship unknown	4 (1.2%)	2 (1.1%)	2 (2.9%)

serologic test or by the development of syphilitic manifestations. On the women, in only 6 was the time of onset known and this number is too small to be of statistical significance. Table 11 breaks up into decades the time of onset of syphilis in both sexes. For the entire group the median age of onset is 26 years, which is what one would suspect from any large group of syphilitic patients. For comparison with non-diabetic patients we have been able to find a series of 6186 cases of

syphilis in male patients reported to the Massachusetts Department of Public Health,³⁶ but these are only for cases of early syphilis. Except for the years 15 to 19 there is about the same incidence in all decades. Thus it would appear that in diabetic and in nondiabetic patients the average age at which the onset of syphilis occurs is about the same.

Maximum Weight—The role of obesity has long been prominent in the study of diabetes, particularly in the adult patients. Very frequently diabetic patients give a history of obesity prior to the onset of diabetes. Of all diabetic patients a careful record has been made of previous weights. Table 12 in detail compares by sex the maximum weight of 207 diabetic patients having syphilis with a group of 4,596 diabetic patients. These figures show a remarkable similarity and indicate that diabetic patients with syphilis and other diabetic patients have as a very prominent feature of their metabolic disease a common factor of obesity. Apparently in diabetic patients with syphilis the presence of syphilis has no relationship to the diabetes. As a miscellaneous item included in the table are figures for the weight of the diabetic patients with syphilis at the time of the first visit.

Priority of Syphilis—Naturally, in a suspected relationship between syphilis and diabetes the entire subject centers on the priority of syphilis. In table 13 our cases have been classified as to priority. In certain cases the patients were definitely known to have had syphilis prior to the onset of diabetes. In addition, there were some cases in which, according to the history, there was little doubt that syphilis preceded the diabetes, and these were classified as "probable" cases. In some cases it was impossible to determine any time relationship. To us, the fact that syphilis precedes diabetes in the majority of cases is not startling. In general, syphilis is a disease acquired in youth and diabetes is a disease developing in an older age period.

Priority of Diabetes—Of the entire number of 258 patients with syphilis, there were 5 male patients (1.9 per cent) whose syphilitic infection was known to have occurred after the onset of the diabetes. In none of these patients did the onset of syphilis seem to aggravate the diabetes. Limitation of space forbids presentation of their case histories.

Duration of Syphilis Prior to Onset of Diabetes—A determination of the duration of syphilis (in the cases in which the date of the onset of the infection is known) until the time of onset of the diabetes is of significance in showing the stage of the syphilis that is usually present when diabetes appears. We have been able to do this in 107 cases, and the figures are very interesting. Table 14 shows that in only 1.9 per cent of the total cases did diabetes appear in a three year period after the onset of

³⁶ Howard, E. B. Reported Gonorrhea and Syphilis in Massachusetts, 1930-1937, *New England J. Med.* **219**: 639-644 (Oct. 27) 1938.

the syphilitic infection, and in only 19 per cent did diabetes appear in the three to six year period. In all the rest, diabetes appeared at least six years after the patient became syphilitic. On the average, the men had had syphilis twenty-one years before the onset of diabetes and the women had had it for fifteen years.

Duration of Diabetes Until Death—Table 15 shows that in 130 fatal cases, the total average duration of life from the onset of diabetes to death was nine and six-tenths years. When the data are broken up on the basis of sex, it is seen that the men on the average lived ten

TABLE 14—*Duration of Syphilis*^{26a} (in Cases of Known Priority) at Time of Onset of Diabetes¹

Duration	Per Cent			Number		
	Total	Male	Female	Total	Male	Female
Total	100.0	100.0	100.0	107	90	17
Less than 3 years	1.9	2.2		2	2	
From 3 years to 6 years	1.9	2.2		2	2	
From 6 years to 9 years	4.7	5.6		5	5	
From 9 years to 12 years	7.5	5.6	17.6	8	5	3
From 12 years to 15 years	8.4	10.0		9	9	
From 15 years to 20 years	12.1	13.3	5.9	13	12	1
From 20 years to 25 years	10.3	11.1	5.9	11	10	1
From 25 years to 30 years	9.3	10.0	5.9	10	9	1
From 30 years to 40 years	8.4	10.0		9	9	
From 40 years to 50 years	3.7	4.4		4	4	
Unknown	31.8	25.6	64.7	34	23	11
Average duration in years				20	21	15

TABLE 15—*Duration of the Disease in Years and by Sex From Onset to Death Among One Hundred and Thirty Deceased Diabetic Patients With Syphilis*

Disease	Total	Male	Female
Diabetes	9.6	10.0	8.6
Syphilis	30.0	30.0	31.0

years and the women eight and six-tenths years. As compared with all diabetic patients^{26a} these durations are longer because of the fact that they are drawn entirely from older patients, diabetes being generally less severe in older than in younger patients.

Duration of Syphilis Until Death—Table 15 shows that the average duration of syphilis is thirty years for male patients and thirty-one for female patients. It is obvious that diabetes is a further burden on syphilitic patients and in many cases shortens the duration of life.

Severity of Diabetes—The criteria for estimation of the severity of the diabetes were given in a preceding section. In table 16 the cases are so classified. Between the sexes there is no real difference of statistical significance. A comparison of severity with that in diabetic patients

without syphilis classified on the same criteria would be interesting, but we have never studied our whole group of diabetic patients in just this way, nor have various authors in the literature. However, judging from our experience with diabetic patients, we do not believe patients with syphilis have diabetes in any milder or in any more severe form than nonsyphilitic patients of the same age. If they seem to have milder diabetes, the reason is that the patients with that form are from the older age groups, in which diabetes generally is less severe. We have no real evidence that syphilis aggravated the severity of the diabetes in the cases in which a diabetic patient later became syphilitic.

TABLE 16—*Severity of Diabetes Among Diabetic Patients With Syphilis*

Severity	Per Cent			Number		
	Total	Male	Female	Total	Male	Female
Total	100.0	100.0	100.0	258	188	70
Mild	65.9	68.6	58.6	170	129	41
Moderate	19.0	16.5	25.7	49	31	18
Severe	8.9	9.0	8.6	23	17	6
Unknown *	6.2	5.8	7.2	16	11	5

* Includes 8 cases observed before the discovery of insulin.

TABLE 17—*Degree of Control of Diabetes Among Diabetic Patients with Syphilis*

Control	Per Cent		
	Total	Male	Female
Good	41.9	46.8	28.6
Fair	29.5	25.0	41.4
Poor	15.9	14.4	20.0
Unknown	12.8	13.9	10.0

Degree of Diabetic Control—Using the criteria for diabetes under good control as given previously, the cases were classified arbitrarily as being generally under good, fair, poor or unknown control (table 17). Of course such an estimation involves a marked personal factor, but this phase of the subject has only slight bearing on the problem of showing if there is a relationship between diabetes and syphilis. We do not have available a similar study of our whole group of diabetic patients and therefore cannot make comparisons with a general diabetic population.

Heredity of Diabetes—As a factor in the causation of diabetes, heredity plays a most important part. Much work has been done in securing detailed case histories with continuous follow-ups, especially for diabetic children enabled to live after the discovery of insulin, and that work has shown that it is "highly probable that the development

of diabetes depends primarily upon the transmission of a single recessive gene and the operation of one or more secondary factors" ^{26a}

Can it be shown that diabetic patients with syphilis have a different hereditary background from diabetic patients without syphilis? Table 18 shows that including both hereditary and familial heredity, in 26.7 per cent of the cases the patients gave a history of diabetic heredity. This percentage is the same as in the whole group of diabetic patients, because between 1897 and 1928 there were 6,357 diabetic patients, and the total incidence of diabetes in their families was 24.5 per cent.

The part that heredity plays can be studied in other ways. The syphilitic patients have been divided further into those with a positive diabetic heredity and those with a negative diabetic heredity, with distinctions made for the severity of diabetes, the incidence of diabetic coma and the presence of acetone bodies in the urine at any examination. Patients without a heredity history for diabetes had more severe diabetes, a higher incidence of diabetic coma and more frequently had

TABLE 18—*Patients With Positive Heredity History for Diabetes*

	Number of Patients	Heredity Present	Per Cent
Total	258	69	26.7
Male	188	47	25.0
Female	70	22	31.4

acetonuria than patients with such a history. In this sort of comparison diabetic patients with syphilis are no different from those without syphilis. At first one might suppose that patients with a diabetic heredity would tend to have a more severe type of diabetes. As early as 1923 ³⁷ it was pointed out that patients with a diabetic heredity usually had a milder type of diabetes, with a slightly longer duration of diabetic life, than patients without such heredity. This is so, because diabetic relatives of a patient slowly appear as life progresses, the longer a diabetic patient lives (and thus appears to have a milder condition) the more likely that diabetes will develop in a relative, and consequently the longest living patients have the greatest hereditary history of diabetes. From these studies of heredity we cannot say that diabetic patients with syphilis differ from diabetic patients without syphilis.

Hereditary Syphilis—White ³⁸ in 1932 reported that in 440 juvenile diabetic patients she found no evidence of syphilis. Our experience with

³⁷ Joslin, E. P. *Treatment of Diabetes Mellitus*, ed. 3, Philadelphia, Lea & Febiger, 1923.

³⁸ White, P. *Diabetes in Childhood and Adolescence*, Philadelphia, Lea & Febiger, 1932.

diabetic children is drawn from this same group, now grown to 1,400 in number. With this increase in the number of cases there have appeared 3 cases of congenital syphilis, as would almost be bound to happen in such a large group of children. We regret that lack of space forbids detailed discussion of these cases and also that a review of the literature pertaining to congenital syphilitic children with diabetes must be omitted. In brief, we have not found that syphilis plays any part in the causation of childhood diabetes in this large group of juvenile patients.

Conjugal Diabetes and Conjugal Syphilis—Table 19 gives the incidence of conjugal complications. In the total number of diabetic patients effort was always made to note the presence of conjugal diabetes, but a list of these patients is not complete. Seventy-two examples of conjugal syphilis in 15,095 diabetic patients is a minimal number. The incidence is therefore 0.48 per cent, which is less than the 0.8 per cent of

TABLE 19—*Incidence by Sex of Conjugal Diabetes and Syphilis and of Hereditary Syphilis Among Diabetic Patients With Syphilis*

	Per Cent			Number		
	Total	Male	Female	Total	Male	Female
Total, all patients				258	188	70
Conjugal diabetes	0.8	1.1		2	2	
Conjugal syphilis	2.7	0.5	8.6	7	1	6
Conjugal diabetes and syphilis	0.4	0.5		1	1	
Hereditary syphilis	1.2	0.5	2.9	3	1	2

syphilitic patients, but the numbers are too small to be of statistical significance. In the series there is 1 set of marriage partners with both syphilis and diabetes. Curschmann³⁹ mentions 2 such sets. Of our cases 6 diabetic women had conjugal syphilis, as contrasted with only 1 diabetic man. Three of the women had a positive heredity history for diabetes, the man did not have such a history.

A study of the cases of conjugal diabetes and syphilis has really surprised us, because of the following facts in relation to neurologic complications of the syphilis in these few cases. Four of the women had husbands with dementia paralytica, but only 1 of these women had syphilis of the central nervous system, and she also had a Charcot joint. Two other women in the series of syphilitic patients also had Charcot's joint. There was a single set of syphilitic mates, both with syphilis of the central nervous system. Of the 8 different patients, 4 had syphilis of the central nervous system. A careful study of these unusual patients does not give any suggestion that syphilis caused diabetes.

³⁹ Curschmann, H. *Über exogene ursachliche Faktoren bei Diabetes mellitus*, Klin. Wchnschr. **13** 511-514 (April) 1934.

Antisymphilitic Treatment—Not all of the patients were treated by us, since many were referred to a syphilologist or to an outpatient department for syphilitic patients or were treated by the referring physician. Some of the elderly patients were not treated, and for about a third of the patients details of treatment were unknown. These may or may not have had treatment and probably had little or none. Table 20

TABLE 20—*Treatment of Syphilis Among Diabetic Patients With Syphilis*

Treatment	Per Cent	Number
Total of patients	100 0	258
Known to have some treatment	59 7	154
Known to have no treatment	4 3	11
Treatment unknown	36 0	93
Where treatment was given		
Total of patients	100 0	154
By us only	3 2	5
Elsewhere	59 1	91
By us and elsewhere	9 1	14
By us and ? elsewhere	27 9	43
Unknown	0 6	1

TABLE 21—*Incidence of Certain Complications Among Diabetic Patients With Syphilis*

	Per Cent			Number		
	Total	Male	Female	Total	Male	Female
Total				258	188	70
Gangrene	8 5	7 4	11 4	22	14	8
Angina	8 1	9 6	4 3	21	18	3
Cerebral hemorrhage	9 7	7 4	15 7	25	14	11 §
Central nervous system (including dementia paralytica, the tabetic form of dementia paralytica and syphilis of the central nervous system)	12 0	12 2	11 4	31	23	8
Cardiovascular syphilis (including aortitis, aneurysm, aortic insufficiency)	5 8	6 9	2 9	15	13 †	2 #
Diabetic neuropathy	3 5	3 7	2 9	9	7 †	2
Hypertension *						
Systolic 150-175	24 8	20 7	35 7	64	39	25
Systolic over 175	8 1	6 4	12 9	21	12	9
High diastolic	1 2	0 5	2 9	3	1	2

* Average blood pressure readings used, when not given, highest reading used

† Includes 3 cases (? aortitis), 1 case (? aortic insufficiency)

‡ Includes 3 cases (? diabetic neuropathy)

§ Includes 1 case (probable)

Includes 1 case (probable insufficiency)

gives the data about how much treatment these patients had. Practically 60 per cent received treatment. Of the treated patients 40.2 per cent received some treatment at our office, and these comprise 24 per cent of the 258 diabetic patients with syphilis. In a following section of this paper, details will be given concerning the results of the antisymphilitic treatment of these patients.

Complications Among Diabetic Patients with Syphilis—Table 21 lists the percentage of certain specific complications and of others mentioned in the literature on the combination of the two diseases.

1 Cerebral Hemorrhage Of the total number of 258 diabetic patients, both living and deceased, cerebral hemorrhage occurred in 97 per cent It is impossible to compare these patients with a similar number of all diabetic patients However, if only deceased patients are considered, table 22 shows that of the 130 deceased patients, apoplexy was the cause of death in 13.1 per cent, as compared with 7.1 per cent of patients with all types of diabetes This indicates that, as would naturally be expected in syphilitic patients, cerebral hemorrhage seems to occur more commonly in these older patients, because of the nature of the disease Of course, probably in most cases, the cerebral hemorrhage occurs on a pathologic basis other than that of syphilis

2 Syphilis of the Central Nervous System, Diabetic Neuritis Of the entire group of 258 diabetic patients with syphilis mentioned, 120 per cent were considered to have syphilis of the central nervous system, as diagnosed by examination of the spinal fluid or by the presence of characteristic signs These patients include those with dementia paralytica, the patients with tabes dorsalis and a number whose condition was classified simply as syphilis of the cerebrospinal system Two tabetic patients had a cord bladder These patients do not include a few with cerebral hemorrhage perhaps caused by syphilitic vascular changes within the skull This 12.0 per cent does not differ significantly from the percentage of patients with neurosyphilis in a large number of syphilitic patients in the population of Massachusetts at large,³⁶ because the average of 39,159 cases reported in the state from 1930 through 1937 was 12.5 per cent for males and 5.8 per cent for females

Concerning syphilis and diabetes together, much has been written about loss of reflexes, perforating ulcers, neuralgia, peripheral neuritis, pseudotabes of diabetic patients, coexistent diabetes with dementia paralytica, ocular paralyses and spinal fluid findings In the past few years a type of polyneuritis called diabetic neuritis, or neuropathy, has been described in diabetic patients In the very definite cases of so-called diabetic neuritis that we have observed, besides neurologic findings and neuralgic pains, unlike the crises and other signs of neurosyphilis, the spinal fluid has presented a definite contrasting picture The Wassermann reaction is negative, the cell count is within normal limits, and the total protein content is usually elevated and may be markedly so, being anywhere from 60 to 300 mg per hundred cubic centimeters Of the group of syphilitic patients there were 3 who had suggestive diabetic neuropathy, and these will not be considered There were 6 patients in whom the symptoms were characteristic of diabetic neuropathy In only 3 cases was the spinal fluid examined, and in 2 the Wassermann test of the spinal fluid was negative Space forbids discussion of these cases In the 258 cases of diabetes and syphilis the spinal fluid was examined at

least once in 55 cases, in the great majority of cases, by us. Other than to call attention to the fact that there are abnormalities in the spinal fluid due to diabetic neuropathy which differ from abnormalities due to neurosyphilis, there is no reason in this paper to dwell on the subject further than to say we can find no reason to believe that neurosyphilis causes diabetes.

3 Cardiovascular Syphilis. There was evidence of cardiovascular syphilis in 5.8 per cent of the cases, not including any of cerebral hemorrhage. These cases include those of diabetes with uncomplicated aortitis, with aneurysms and with aortic insufficiency. In 1 case with a negative serologic reaction, typical syphilitic aortitis was found at autopsy by gross appearance, confirmed by the microscopic observations. Since uncomplicated syphilitic aortitis is an asymptomatic condition⁴⁰ and very difficult to diagnose in early stages,⁴¹ it is not unlikely that had some of our patients been observed for a longer period, there would have been a higher percentage of cases of diabetes with cardiovascular syphilis.

4 Angina Pectoris. At least 8.1 per cent of the patients had angina pectoris. This is not surprising in view of the fact that the patients are in the older age groups. It is true that involvement of the ostia of the coronary arteries in syphilitic aortitis may be the source of the production of the pain, but we believe that in practically all cases the angina was related to the age of the patient and to the degree of coronary arteriosclerosis as influenced by the duration of diabetes. The incidence of angina in 10,000 diabetic patients of all types was 4.1 per cent.^{26a} This percentage is lower than that in the syphilitic patients, because so many young diabetic patients are included in the larger series.

5 Hypertension. The criteria for the designation of hypertension have been given. In 33 per cent the systolic blood pressure averaged 150 mm. of mercury. This percentage is not different from that obtained in a similar group of old diabetic patients without syphilis, and, as in them, the percentage of hypertension is related to the known factors of advancing age and increasing arteriosclerosis, plus other unknown factors in the causation of hypertension.⁴²

6 Charcot's Joint. There were 3 patients with Charcot's joint and 2 others in whom the presence of the condition was questionable. Of the 2 patients just mentioned, 1 had tabes and dementia paralytica and a positive reaction of the spinal fluid. In the case of the other patient

40 Wilson, R., Jr. Uncomplicated Syphilitic Aortitis. An Asymptomatic Condition, *Am J M Sc* **194** 174-185 (Aug) 1937.

41 Wile, U. J., and Snow, J. S. Occult Cardiovascular Syphilis, *Am J M Sc* **195** 240-248 (Feb) 1938.

42 Root, H. F., and Sharkey, T. P. Arteriosclerosis and Hypertension in Diabetes. *Ann Int Med* **9** 873-882 (Jan) 1936.

the spinal fluid was not examined, but the history of the difficulty and the appearance on roentgen examination suggested a syphilitic lesion of the bones. Apart from these 5 syphilitic patients there have been Charcot joint lesions in 2 patients with diabetes in whom evidence of syphilis was not proved. Tests of the spinal fluid gave a negative Wassermann reaction in each. One of these patients definitely had diabetic neuropathy.

7. *Gangrene*. Gangrene occurred in 8.5 per cent of the cases. It must be noted that in addition to these cases other cases of gangrene would undoubtedly have occurred if in other cases of infections of the foot among these old patients the lesion had been allowed to progress. This proportion of the incidence of gangrene is no higher than in diabetic patients without syphilis. It has been reported^{26a} that in 323 cases of gangrene the serologic reactions were positive in 1.9 per cent. This is not significantly different from the incidence of syphilis of 1.7 per cent in the entire series of 15,059 diabetic patients. Previously,³⁷ a higher incidence of gangrene (10 per cent) was reported in diabetic patients with syphilis, as compared with 2.8 per cent in all the patients with diabetes, but since that report in 1923, many thousands of patients with diabetes have been seen, and it has been found that syphilis has no part in the production of gangrene. Lemann⁴³ in 1927 came to the conclusion that syphilis does not predispose diabetic persons to gangrene. Of 17 white persons with gangrene, none had a positive Wassermann reaction. There was a preponderating gangrene ratio in the Negro patients, in whom there was also a preponderance of syphilis, but the two diseases could not be found to be etiologically related, since only 2 of 36 Negroes with gangrene (5.5 per cent) had a positive Wassermann reaction, as compared with 6.4 per cent of positive Wassermann reactions in all diabetic Negroes. He believed gangrene in the Negro to be best explained by poor care and hygiene.

Causes of Death.—Does the cause of death throw any light on the question of relationship of syphilis and diabetes? Fortunately for comparison we have the verified statistics for a very large group of deaths in diabetic patients. In table 22 are listed the causes of death in per cent for 130 diabetic patients with syphilis as compared with the causes for 4,474 diabetic patients. By observing the first and last columns, it is seen that there is no essential difference that cannot be easily explained. For example, the fact that only 14.6 per cent of the diabetic patients with syphilis died in coma, as compared with 20.3 per cent of all diabetic patients, is explained in that the latter group contained many juvenile patients, who in the early days before the discovery of insulin

⁴³ Lemann, I. I. Diabetic Gangrene in the South, J. A. M. A. **89** 659-661 (Aug. 27) 1927.

frequently died in diabetic coma. The nearness with which the percentages coincide is really surprising. This certainly suggests that syphilis has little effect on the final outcome of diabetes. Only indirectly is it indicated that syphilis has no part in the causation of diabetes. It must be admitted that if there were a rare case of diabetes caused by

TABLE 22—*Causes of Death of Diabetic Patients With Syphilis, Comparison by Sex With Causes of Death in Percentage of All Diabetic Patients*

Cause of Death	Diabetes with Syphilis (1897 1939)						4,471 Diabetic Patients (1897 1939)
	Per Cent			Number			
	Total	Male	Female	Total	Male	Female	
All causes, per cent or number	100 0	100 0	100 0	130	97	33	100 0
Primary coma	10 0	10 3	9 1	13	10	3	} 20 3
Secondary coma	4 6	5 2	3 0	6	5	1	
Cardiorenal vascular disease, total	47 7	46 4	51 5	62	45	17	44 2
Arteriosclerotic	47 7	46 4	51 5	62	45	17	43 8
Cardiac	21 5	23 7	15 2	28	23	5	23 4
Angina pectoris or coronary	13 8	14 4	12 1	18	14	4	
Nephritis	2 3	3 1		3	3		3 6
Apoplexy	13 1	11 3	18 2	17	11	6	7 1
Gangrene	4 6	4 1	6 1	6	4	2	6 7
Multiple or unassigned site	6 2	4 1	12 1	8	4	4	5 7
Nonarteriosclerotic							0 4
Infections, total	15 4	16 5	12 1	20	16	4	13 6
Influenza and pneumonia	7 7	9 3	3 0	10	9	1	6 9
Other infections of the respiratory tract, mastoid, etc	2 3	2 0	3 0	3	2	1	0 8
Appendicitis	1 5	1 0	3 0	2	1	1	0 6
Carbuncle	0 8	1 0		1	1		1 2
Erysipelas	0 8	1 0		1	1		0 3
Abscess of skin, or of other organs	2 3	2 1	3 0	3	2	1	1 5
All other infections							1 8
Tuberculosis	5 4	6 2	3 0	7	6	1	4 9
Cancer	6 9	6 2	9 1	9	6	3	7 6
Syphilis	3 1	2 1	6 1	4	2*	2	
Other causes	11 5	12 4	9 1	15	12	3	
Diseases of prostate gland	0 8	1 0		1	1		
Cirrhosis of the liver	1 5	2 1		2	2		
Acute intestinal obstruction	0 8	1 0		1	1		
Pernicious anemia	0 8	1 0		1	1		
Accidents	0 8	1 0		1	1		1 5
Suicides	2 3	3 1		3	3		0 5
Diabetes	3 1	2 1	6 1	4	2	2	
Other diseases and conditions	1 5	1 0	3 0	2	1	1	

* Syphilitic heart

syphilis, it would not influence these statistics and thereby be evident. This is a very important point to remember.

Of the 130 cases of death, autopsies were done in 21, and not all at our hospital. An aortitis was found in 2 cases and a syphilitic ulcer of the trachea in another. If autopsies had been done in all cases a larger proportion of syphilitic defects would very likely have been found. Previously in this paper,¹⁴ reference was made to the proportion of cases of syphilis found in a large series of autopsies on diabetic patients. Besides syphilitic pathologic changes appearing at autopsy other syphi-

litic degenerations were observed, such as tertiary cutaneous lesions. Three patients had carcinoma of the tongue, the relationship between syphilis and this type of cancer is well known.

Death Rates—Many problems arise in the presentation of accurate mortality data of patients suffering with chronic diseases, particularly as is related to the age at onset of those diseases. The reasons for the method of tabulation as given in table 23 have been summarized elsewhere.⁴⁴ The years of life in which the patient is exposed are the years from the first observation. The patients whose syphilitic infection occurred before the first visit are included in the table from the time

TABLE 23—*Death Rates per Thousand Among Diabetic Patients With Syphilis and Ratio of These Rates to Those for All Male Diabetic Patients and for Males in the General Population*

	Years of Life Exposed *	Deaths	Death Rate per Thousand	Ratio to Death Rate	
				Of Male Diabetic Patients †	Of White Males in the General Population ‡
Deaths in preinsulin era					
All ages	197	17	86.3	0.7	
30-49	74	6	81.1	0.7	
50 and over	121	11	90.9	0.7	
Deaths in insulin era					
Patients first seen prior to Aug. 7, 1922					
All ages	285	25	87.8	1.0	2.5
30-49	49	3	61.2	1.8	6.8
50 and over	221	22	99.4	1.0	2.3
New patients					
All ages	946	76	80.3	1.1	2.8
30-49	233	12	51.4	1.5	6.3
50 and over	702	63	89.7	1.0	2.5

* Patients seen prior to 1938 followed to Jan. 1, 1938. Fractional parts of years of life exposed were tabulated, but the exposed in this table are taken to the nearest whole numbers.
† In same era of insulin experience for all male diabetic patients, 1922-1929.
‡ Massachusetts, 1929 to 1931.

of the first visit, those few in whom the infection occurred at some time afterward are included only from the reported date of infection. Patients first seen with grave complications which were almost immediately fatal have been excluded. Comparisons with the death rates of nonsyphilitic patients have been made with the rates as computed for male patients, since most of the deaths among diabetic patients with syphilis were in male patients.

Ratios under 1 indicate a lower death rate in the group with syphilis, and ratios in the neighborhood of 1 indicate approximately the same mortality. The lower death rate in the preinsulin area is explained by

44 Joslin, E. P., Dublin, L. I., and Marks, H. H. Studies in Diabetes Mellitus. VI. Mortality and Longevity of Diabetics, *Am. J. M. Sc.* **195**: 596-608 (May) 1938.

the fact that before insulin was used the ordinary diabetic patient without the protection of insulin had a much shorter duration of life. As we have shown, the diabetic patients with syphilis are the older ones, who usually have less severe diabetes, and this factor has been constant throughout the years. Now that the other diabetic patients with the proper use of insulin can have a more nearly normal life expectancy, the statistics show that syphilis is a further burden to a diabetic patient and tends to decrease the life expectancy.

OTHER ASPECTS OF COEXISTENT DIABETES AND SYPHILIS

Experimental Diabetes and Syphilis—The only reference found to this subject was an abstract by Lemann³ of work done by Memmesheimer, who first made rabbits diabetic by pancreatectomy and then inoculated them with syphilis. The conclusion reported was that the diabetes was not made more severe by the syphilis and that the course of syphilis in the depancreatized animals was no different from that in the nondiabetic animals.

Immunity—Various authors have mentioned that if diabetes is caused by syphilis, a diabetic patient should be immune to further attacks of syphilis. Not many diabetic patients get syphilis, because at the age that diabetes usually appears the patients are beyond the age at which syphilis is usually contracted. Furthermore, many diabetic patients are impotent. In a previous paragraph, in the discussion of the priority of diabetes, mention was made of 5 cases in which a diabetic patient later became syphilitic. It is certain that patients with diabetes are not refractive to syphilis.

Prognosis—Our cases really indicate that diabetes and syphilis have so little relationship that the prognosis for a person suffering from both diseases is a summation of the prognoses for the two diseases. Since both are chronic diseases of long duration, it is inevitable that some patients acquire both diseases. Syphilis on the average shortens a person's life for a certain number of years, and diabetes has the same action. Apparently there is no synergistic effect.

COMMENT

The possible relationship of diabetes and syphilis does give opportunity for interesting speculations. Using rigid criteria fulfilled by every case, we have presented a large series of diabetic patients who also had syphilis. It is important to note that in most cases the courses of the two diseases were followed for many years. The 258 cases have been examined in great detail and only in such a large series is it possible to study certain fundamental aspects of the problem of the relationship of diabetes and syphilis.

The average incidence of syphilis in diabetes (17 per cent) has been essentially the same in the diabetic patients in our practice when the number is broken up into groups of nearly a thousand each and is less than in the general population of this locality. When first observed concerning the diabetes, almost 87 per cent of the patients were in the latent stage of syphilis. Race or nationality is of little bearing in the problem except that the Jewish race, with a higher incidence of diabetes in comparison to the proportion in the general population, definitely had fewer syphilitic members in proportion in the syphilitic practice.

A very valuable point shown in this study is the fact that the age of onset of diabetes is the same in diabetic patients with syphilis as in all diabetic patients, in the various decades in which diabetes may appear. On the other hand, the average age at onset of syphilis is the same as for the whole population.

The factor of obesity has long been known to play an important part in the causation of diabetes. Comparison of the diabetic patients with syphilis with all diabetic patients has shown a surprising similarity in their respective weights at the onset of diabetes.

If syphilis causes diabetes, it is obvious that syphilis must precede the onset of diabetes. Of all the cases there were only 5 in whom a diabetic patient subsequently acquired syphilis, and there were 2 doubtful cases. In all the rest there was but little doubt that syphilis was present before the onset of diabetes. The long duration of syphilis before the onset of diabetes in the great majority of cases (over six years in 96 per cent of the cases) certainly indicates that if there is any relationship between the two diseases, diabetes is a tertiary or late manifestation of the syphilis. Incidentally, if syphilis does cause diabetes, why does not the diabetes appear at about the same average age in each sex? No evidence of a relationship between the two diseases is afforded by this analysis, because there is a difference of six years between the sexes in the duration of syphilis before the onset of diabetes.

It has been shown that the duration of diabetes is longer in diabetic patients with syphilis than in other diabetic patients, because the patients selected on the bases of the presence of syphilis are older and have generally milder diabetes than the younger patients, who are automatically excluded except for the rare ones with hereditary syphilis.

The most important factor in the causation of diabetes is heredity. If there is less history of diabetes in the heredity of diabetic patients with syphilis than in diabetic patients without syphilis, this would tend to indicate that in these patients with the two diseases syphilis might play an etiologic role. Such is not the case, for it has been shown that the heredity for diabetes is the same.

If there is any type of syphilis in which diabetes should be produced (and if it is possible to cause diabetes), it is congenital syphilis, for in this condition the pancreas is much more frequently involved than in acquired syphilis and there is a much greater chance for syphilis to destroy the islands of Langerhans. An estimate has been made⁴⁵ that in this country 60,000 infants with congenital syphilis are born each year. If there were some relationship between diabetes and syphilis, this number of syphilitic infants should certainly have some influence on the incidence of diabetes in childhood. As a main point for arguing that congenital syphilis is the cause of diabetes in children Mikulowski⁴⁶ used the fact that so many anomalies and malformations appear in diabetic children, as pointed out by Priesel and Wagner⁴⁷. He stated that syphilis is the most important factor for all the congenital anomalies and malformations and that many of the malformations of juvenile diabetes are also characteristic of congenital syphilis. It is true that malformations frequently appear in diabetic children, and, incidentally, also they appear frequently in the babies of diabetic mothers, but we see no evidence for this suggested relationship. Both White⁴⁸ and Wagner,⁴⁸ who have probably seen more children with diabetes than any other diabetic specialists, have stated that the abnormalities found in diabetic children are not the kind found in syphilitic children. Mikulowski also reported that in ten years he had studied 80 syphilitic children, finding in 70 per cent that by a dextrose tolerance test (50 Gm) hyperglycemia was produced (no figures given), and that the blood sugar content returned to normal after antisyphilitic treatment. He likened this abnormality to that of true diabetes and attributed it to hepatic insufficiency from syphilitic involvement. However, Mikulowski had never seen a cure of supposed syphilitic diabetes in a child. Labbé and Toufflet² stated that they had never observed improvement in a diabetic child who was given antisyphilitic treatment and that they had treated several.

A general discussion of antisyphilitic treatment for diabetic patients is intimately related to many comments already made in the presentation of Troller's postulates, and these should be reviewed. In these days one should have definite criteria to conform to in order to avoid false conclusions. Above all, a diabetic patient with syphilis should be first stabilized on a diabetic regimen before antisyphilitic therapy is instituted.

45 Parran, T, cited by Whipple, C V, and Dunham, E C. Congenital Syphilis. II. Prevention and Treatment, *J Pediat* **13** 101-119 (July) 1938.

46 Mikulowski, V. Le problème de l'étiologie syphilitique du diabète infantile, *Rev franç de pédiat* **9**:767-782, 1933.

47 Priesel, R, and Wagner, R. Fehlbildungen beim Diabetes mellitus der Jungendlichen, *Ztschr f Kinderh* **49** 419-428, 1930.

48 White, P, and Wagner, R. Personal communications to the authors, 1939.

and the results interpreted Too often antidiabetic and antisyphilitic treatments are started simultaneously, which makes proper interpretations of results impossible A review of the literature shows that the more recent the cases in past years (i e, since the time of the discovery and use of insulin with more normal diets), the fewer the number of cases in which the condition seems to be improved by antisyphilitic treatment Specialists in their fields, such as Labbé and Toufflet,² Moore,⁶ Naunyn,¹⁰ Bertram,⁴⁹ von Noorden,⁵⁰ Lemann,³ Rosenbloom⁴ and others,⁵¹ have not seen any definite cure of diabetes by antisyphilitic treatment, or even slight improvement in the diabetes except in rare cases

However, as Brandau⁵² has stated, patients with diabetes in whom syphilis is proved or suspected should be given the benefits of antisyphilitic treatment for its possible good effect on the diabetes, as well as for its general antisyphilitic value Common sense would tell a physician not to start antisyphilitic therapy of diabetic patients, especially of those with severe types, until after the diabetes is under control An exception pointed out by Stokes⁵ would be a patient with a seronegative primary lesion, for whom immediate institution of therapy is important In most cases the few days of delay for diabetic regulation is of no significance Stokes said that in patients with late diabetes of the relatively benign type he had never seen evidence of reduced tolerance to arsphenamine or unfavorable reaction to other forms of treatment for syphilis Moore⁶ has expressed similar opinions, he observed that the coexistence of diabetes is no contraindication to energetic antisyphilitic treatment, provided the diabetes can be controlled Lapp and Schwarz⁵³ did not find diabetes a contraindication to malaria therapy for syphilis of the central nervous system, though they found during the treatment a rise in the sugar content of the urine and of the blood, such as might be found in any febrile disease, except that there was no acetonuria, and after termination of the paroxysms there was a rapid return of the diabetic status to the former level, as contrasted with what usually occurs after fever of other origin Stokes says patients with severe diabetes should not be given treatment for malaria In our diabetic patients we have not found any contraindications to antisyphilitic treatment Naturally a diabetic patient with syphilis should be considered

49 Bertram, F Die Zuckerkrankheit, Leipzig, Georg Thieme, 1933, p 32

50 von Noorden, C, and Isaac, S Die Zuckerkrankheit und Ihre Behandlung, ed 8, Berlin, Julius Springer, 1927, p 350

51 Elmer and Kedzierski¹⁸ Mikulowski⁴⁶

52 Brandau, G M Diabetes Mellitus of Syphilitic Origin, Am J Syph 16 511-518 (Oct) 1932

53 Lapp, F W, and Schwarz, H Malaria Treatment of Neurosyphilitic Diabetics, Wien med Wchnschr 82 1599-1605 (Dec 24) 1932

like any patient concerning possible risks before an antisyphilitic program is planned, and this is particularly applicable to diabetic patients, who are usually in the older age group

The criteria for adequate, or better for optimal, treatment have been given in a preceding section. Using such standards, any physician treating syphilis knows how difficult it is to see that a patient completes a prescribed plan of treatment satisfactorily. We do not believe our diabetic patients with syphilis in this regard have differed much from any group of syphilitic patients. It has been stated that only 16 per cent of persons acquiring syphilis receive enough treatment to reverse the reaction to a serologic test⁵⁴. On the other hand, there are patients who are spontaneously cured of the syphilis without any antisyphilitic treatment, and these are variously estimated up to 30 per cent. In carefully reviewing our own cases we find that very few have received optimal treatment according to our criteria. Many patients have been observed and treated for far too short a period to permit conclusions as yet. If we hold to our criteria for preliminary regulation on a diabetic regimen, the results of antisyphilitic treatment have been practically 100 per cent disappointing.

Altogether, there were 46 patients with treatment in whom the positive serologic reaction became negative. Thirty-nine of these did not receive what has been outlined as optimal treatment. However, it is not necessary to assume that in all of these the serologic reversal took place because of the treatment given, because in most of them the diabetes appeared years after syphilitic infection appeared and was treated, and probably in many the serologic reaction would have become negative anyway with the passage of time. In none of these 46 cases was there any evidence that syphilis aggravated the diabetes, because, in the first place, the syphilitic infection in the great majority of cases was at its most active stage years before diabetic manifestations became apparent and, in the second place, a syphilitic infection does not usually have the toxic febrile reaction of a pyogenic infection which so frequently upsets diabetic control. Also, there was no evidence that the treatment for syphilis given during the time the patient was diabetic in the few cases in which these periods came together caused any improvement in the diabetes. In no case was the carbohydrate tolerance improved above that which would be expected with diet alone or with diet and insulin except possibly in 1 case, in which improvement was temporary. The fact must not be overlooked that occasionally in nonsyphilitic diabetic patients there may be periods in which a patient with mild diabetes,

54 Vonderlehr, R. A., and Usilton, L. J. Syphilis—Chance of Acquisition and the Frequency of Its Disastrous Course, *New York State J. Med.* **38** 1376-1382 (Nov. 1) 1938.

usually requiring insulin, may temporarily not require it. In many instances the diabetes was so mild that changes in carbohydrate tolerance would have been difficult to detect. In some cases the diabetes became gradually worse in spite of treatment. In many cases of the entire syphilitic group the answers to the questions of whether antisyphilitic treatment improved either the syphilis or the diabetes had to be marked "unknown" instead of "yes" or "no."

In addition to the 46 cases with reversal of positive serologic reaction, there were 8 cases in which we considered the patient to have had optimum treatment, and in these the reaction remained positive. Besides these 8 cases there were 7 others in which the patients were considered "probably" to have had the optimum treatment, and in these the serologic reaction was reversed.

A surprising observation was that in 6 cases the glycosuria first appeared while the patient was undergoing antisyphilitic treatment. In 5 of these cases it was with an arsenical preparation, and once it was with iodides. If one were inclined to believe that syphilis did cause diabetes, this mode of onset of the diabetes could perhaps be explained as being due to the "Herxheimer reaction," the therapy having caused a flare-up of the syphilis in some vital organ, such as the pancreas, in these cases. Of these 6 cases there was a history of hereditary diabetes in only 1 case, but in general the patients displayed pretty much the same characteristics as other diabetic patients so far as age at onset and overweight before onset were concerned. In no case did continued antisyphilitic therapy improve the diabetes, which definitely persisted. There were 4 cases in which there were either secondary or tertiary cutaneous lesions, and because of the therapy received, in no case the optimum amount, the cutaneous lesions promptly healed, but the diabetes was not improved. In our experience antisyphilitic therapy has failed in every case to affect the diabetes permanently.

For those authors who would emphasize the frequency with which neurosyphilis causes diabetes, no support is found in this large group of diabetic patients with syphilis. It must be remembered that neurologic abnormalities, such as pupillary and other reflex changes, are not uncommon in diabetic patients without any evidence of neurosyphilis or any type of syphilis, and that when they occur they certainly should not be attributed to syphilis.

The comparative absence of the common sequelae of syphilis, is confirmatory evidence of the infrequency of syphilis as an etiological factor in diabetes. If syphilis is of etiological importance in diabetes, the diabetic possesses remarkable immunity to its customary manifestations.^{26a}

The foreign literature has several times mentioned the possibility of finding a clue to the relationship of syphilis and diabetes in a study of

the cases of married patients. To us there seems to be no relationship. Husband and wife can both become diabetic, we believe, by hereditary predisposition on each side, with the diabetes precipitated in most cases by the development of obesity, it is also common to see marriage partners grow fat together, eating at a common table well stocked with food. As regards conjugal syphilis, it is bound to happen not infrequently that a marriage partner will infect the other, though the chance of infectivity is slight after the third year. The appearance of both diabetes and syphilis in husband and wife must be a rare chance finding, with the syphilis playing no role in the development of diabetes, unless like a pyogenic infection it behaves as a precipitating agent in a married pair each predisposed to diabetes.

Did syphilis seem to cause diabetes in any case? After a careful review of all 258 cases we cannot say that in a single case the history of syphilis and the mode of onset of the diabetes had any definite significance in seeming to point to syphilitic origin of the diabetes. Of course, if one should believe that diabetes is a tertiary lesion of syphilis, then the records would show that in practically all the cases diabetes was due to syphilis, except for those few in which the diabetes definitely began before the syphilitic infection took place and for those cases in which the time relationship could not be determined. It is naturally much easier to see a possible relationship in these cases in which the diabetes has its onset in a short period after the known onset of the syphilis, though when the idea is pursued on a pathologic basis, it would seem more logical for the diabetes to begin late in the course of syphilis, when scarring and fibrosis had produced widespread damage in the pancreas. Of the cases in which the symptom complex of diabetes developed very soon after the initial syphilitic infection, Lemann³ raised the question whether the diabetes might actually be referred to the syphilis, because he said that these cases must not be confused with cases in which a slight transient glycosuria occurs in early syphilis and in which no other diabetic phenomena develop, since such possible cases should never be considered as cases of true diabetes. He quoted Manchot who noted transient glycosuria 17 times in 359 cases of syphilis, with the exact significance of the slight glycosuria not being clear. Continuing, Manchot suggested the glycosuria might be due to a transient reparable disturbance of the pancreas and also of the liver, the disturbance being analogous to syphilitic albuminuria, syphilitic icterus, secondary syphilitic articular and tendon sheath conditions and acute heart failure of syphilitic subjects. Lemann brought out a valuable point in suggesting that when the diabetic symptom complex develops early in syphilis was not there a diabetic background already preexisting with syphilis simply playing the role of a precipitating cause? Very little

has appeared in the literature stating what the effects of antisyphilitic therapy might be in the production of glycosuria in a patient supposedly without diabetes. Modern syphilologists say nothing about a possible effect of antisyphilitic treatment on carbohydrate metabolism to result in the finding of glycosuria in routine analyses of the urine. It is possible that in some cases either mercury or arsenic, by a toxic action on the liver or possibly on the pancreas, could produce glycosuria. If proper criteria are adhered to, it is unlikely that a diagnosis of true diabetes would ever be made in such a case. In relation to this topic there were mentioned 6 patients in whom glycosuria developed while they were receiving antisyphilitic treatment. Subsequently the sugar metabolism of these patients behaved just as it does in any patient with diabetes. Except possibly for these patients, in none of our treated patients did antisyphilitic therapy with arsenicals or bismuth preparations seem to upset the glycoregulatory mechanism.

Of all the 258 cases, there are only 6 in which there is even the slightest suspicion that syphilis caused the diabetes. Though we could say that in none of our cases did syphilis cause diabetes, that still does not preclude the possibility that syphilis might cause diabetes by action on the pancreas, the nervous system or the endocrine glands. Though there have been occasional reports in the literature of cases in which diabetes was caused by syphilis, we have not observed such a case and think it strange, if such cases occur, that we have not met with one in such a large series of proved cases of diabetes. If there is such a thing as "syphilitic diabetes," we have not been able to recognize the characteristics. To us, a patient with syphilis does not have any different type of diabetes than the usual patient of the same age.

In recent years important new researches in the etiology of diabetes have been made. These studies are the valuable observations of Houssay⁵⁵ and Young,⁵⁶ which show the role of the pituitary gland in relation to diabetes. These studies take even further away any thought that syphilis can cause diabetes, unless there might be syphilitic involvement of the pituitary gland, as could possibly occur in basilar meningitis but this is extremely unlikely.

CONCLUSIONS

A careful study of 258 patients with diabetes and with syphilis from a total of 15,095 patients with diabetes has been presented. All have met specific criteria for diagnosis.

⁵⁵ Houssay, B. A. What We Have Learned from the Toad Concerning Hypophyseal Functions, *New England J. Med.* **214** 913-926 (May 7) 1936.

⁵⁶ Young, F. G. Permanent Experimental Diabetes Produced by Pituitary (Anterior Lobe) Injections, *Lancet* **2** 372-374 (Aug. 14) 1937.

A review of cases presented in the literature as instances of diabetes due to syphilis shows that practically all of them fail to satisfy the criteria we have set as being essential for proof of this relationship

The chief factors in the causation of diabetes (positive heredity history of diabetes, the state of being overweight and the age at onset of diabetes) have been shown to be the same for diabetic patients with syphilis as for diabetic patients without syphilis

If "syphilitic diabetes" occurs, theoretically it would most likely be a late manifestation of syphilis occurring in older persons, except in patients with congenital syphilis, in whom diabetes is uncommon

Part of the evidence against the relationship of the two diseases is the fact that there is a marked difference between the sexes in the duration of syphilis before the onset of diabetes

For evaluation of results of antisyphilitic therapy, a diabetic patient with syphilis must be regulated on a constant diabetic regimen

A diabetic patient with syphilis may be given antisyphilitic treatment with the same considerations given to any patient concerning the plan of treatment

To be certain that antisyphilitic treatment has improved or cured diabetes, a case must be followed for years and the condition checked with dextrose tolerance tests

In this series of 258 patients there has not been a single instance of cure of diabetes brought about by optimum antisyphilitic treatment

On the average, a patient with syphilis and diabetes does not appear to have any type of diabetes different from that of the usual patient of the same age

We have not been able to recognize the characteristics of such a clinical entity as "syphilitic diabetes"

ELECTROLYTE BALANCE DURING TREATMENT, CRISES AND SEVERE INFECTION IN CASES OF ADDISON'S DISEASE

ACTION OF ADRENAL CORTICAL EXTRACTS

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The action of adrenal cortical extract and the cause of crisis in Addison's disease are still not understood. The disturbance in sodium chloride metabolism was pointed out by Loeb¹ when he observed the beneficial effect of the administration of these electrolytes. Later, Harrop and his co-workers² showed that alteration of the sodium metabolism was the more important of the two. The importance of disturbed potassium metabolism in patients has been emphasized by Wilder and his associates³ and by Zwemer and Truszkowski⁴. A study of the sodium, potassium and chloride excretion of 2 patients with Addison's disease showed several points of interest and prompted this report.

Both patients had undoubted moderately severe Addison's disease, and they had not received any previous treatment. The first was a youth 18 years of age and the second a woman 24 years of age. The first patient was studied for one hundred and fifty-nine consecutive days and the second for thirty-eight days. Each patient received daily 2 Gm of potassium, 2.36 Gm of sodium, 3.64 Gm of chlorides and sufficient calories in the diet. Extra sodium and chloride were administered in a flavored solution of sodium chloride, sodium citrate and dextrose. The twenty-four hour output of urine was collected daily.

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1 Loeb, R. F. Effect of Sodium Chloride in Treatment of a Patient with Addison's Disease, *Proc Soc Exper Biol & Med* **30** 808-812, 1933

2 Harrop, G. A., Soffer, L. J., Nicholson, W. M., and Strauss, M. Studies on the Suprarenal Cortex. IV. The Effect of Sodium Salts in Sustaining the Suprarenalectomized Dog, *J Exper Med* **61** 839-860, 1935

3 Wilder, R. M., Kendall, E. C., Snell, A. M., Kepler, E. J., Rynearson, E. H., and Adams, M. Intake of Potassium, an Important Consideration in Addison's Disease. A Metabolic Study, *Arch Int Med* **59** 367-393 (March) 1937

4 Zwemer, R. L., and Truszkowski, R. The Importance of Corticoadrenal Regulation of Potassium Metabolism, *Endocrinology* **21** 40-49, 1937

The chlorides were measured by the Volhard-Haivey method⁵ The urine was ashed for sodium and potassium analysis⁶ according to the method of Sholte The former was measured by the technic of Salt⁷ and later by that of Breh and Gaebler⁸ The daily level of urinary creatinine was used as a criterion of complete collections of urine

OBSERVATIONS

Storage of Sodium—It is now generally agreed that there is a loss of sodium from the body in the presence of untreated adrenal cortical insufficiency in animals and in man A partial depletion of sodium would be expected, therefore, in untreated patients Both of our patients showed such a depletion They stored large amounts of sodium at first, after a high sodium intake, and later the rate of storage declined until there was an approximate balance Accompanying this storage of sodium there was a gain in body weight, which reached a plateau simultaneously with the occurrence of sodium balance A reduction of daily sodium intake in 1 patient from 12.58 Gm to 7.67 Gm did not alter the sodium balance or the body weight A further reduction to 2.36 Gm, however, resulted in loss of sodium from the body and a decrease in body weight The patient remained under treatment with this regimen for fifty-four consecutive days, on forty-four of which no cortical extract therapy was given A constant sodium depletion occurred, averaging 1 to 2 Gm daily An increase of the daily sodium intake to 12.58 Gm again resulted in storage of sodium and increase of body weight comparable to the previous results, until a sodium balance was reached, and simultaneously the body weight became constant It required thirty-four days to correct the sodium depletion the first time in our first patient, twenty-seven days the second time and twenty-four days in our second patient It is to be noted from chart 1 that the storage of sodium and the body weight closely paralleled each other

These observations indicate that sodium depletion should be corrected in all patients with Addison's disease, that twenty to thirty days are required for this correction and that changes of body weight are good criteria of sodium loss, storage or balance provided the diet is adequate and constant Storage of sodium is shown by a gain in body weight, loss of sodium by decrease of weight and sodium balance by constant weight

5 Hawk, P. B., and Bergeim, O. *Practical Physiological Chemistry*, ed 11, Philadelphia, P. Blakiston's Son & Co., 1937, pp 769-770

6 Peters, J. P., and Van Slyke, D. D. *Quantitative Clinical Chemistry*, Baltimore, Williams & Wilkins Company, 1932, vol 2, p 70

7 Salt, P. W. A New Triple Acetate Method for Sodium Determinations in Biological Materials, *J Biol Chem* **96** 659-677, 1932

8 Breh, F., and Gaebler, O. H. The Determination of Potassium in Blood Serum, *J Biol Chem* **87** 81-89, 1930

Action of Cortical Extracts—Hariop and his associates² showed that cortical extracts help the body to retain sodium in the presence of adrenal cortical insufficiency. There has not been any attempt, however, to ascertain whether this action of the extracts is altered by storage or loss of sodium from the body or by sodium balance. Hartman, Lewis and Toby⁹ reported decreases of sodium excretion after injections of cortical extracts into normal men and dogs. It is presumed that the adrenal glands and the sodium content of the body were normal. It is to be noted from chart 2 that the effect of cortical extract on the excretion of sodium depends on whether the patient is storing or losing sodium or is in sodium balance, provided the potassium intake is low and constant. After administration of potent cortical extracts there

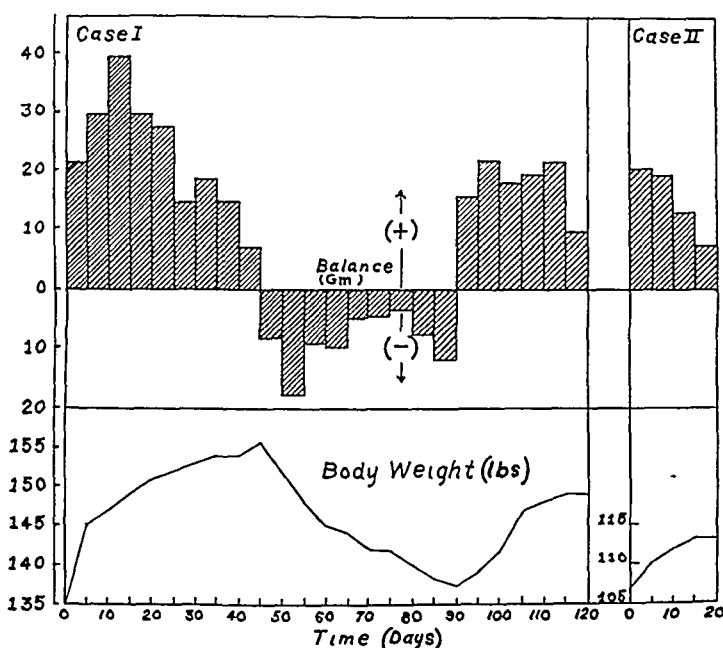


Chart 1—Graph showing the relation of sodium storage or loss of sodium to changes in body weight

was no demonstrable decrease of sodium excretion in our patients when they were in sodium balance or were storing sodium. On the other hand, comparable doses of the extract resulted in definite decrease of sodium excretion during periods when the patient was losing sodium.

These observations indicate that patients with Addison's disease will store sodium at the maximum rate provided the potassium intake is low and constant and the sodium intake is sufficiently large, that under such conditions the administration of cortical extract in therapeutic doses does not accelerate the storage of sodium, and that after sodium

⁹ Hartman, F. A., Lewis, L. A., and Toby, C. G. Effect of Cortin on Excretion of Electrolytes, *Endocrinology* **22** 207-213, 1938

depletion has been corrected cortical extract does not produce any more storage of sodium. On the other hand, the hormone does help the patient to retain sodium when the intake is low and sodium is being lost from the body.

It is possible to obtain data which would indicate that the administration of cortical extracts would produce an increased excretion of sodium. It has been shown in the foregoing paragraphs that the sodium excretion increases as the sodium depletion becomes corrected. If cortical extracts are administered simultaneously with this increased excretion the results are likely to be erroneously interpreted as due to the extract. It is to be noted from chart 2 that sodium retention decreased simultaneously with administration of cortical extract on two occasions, but the decreased

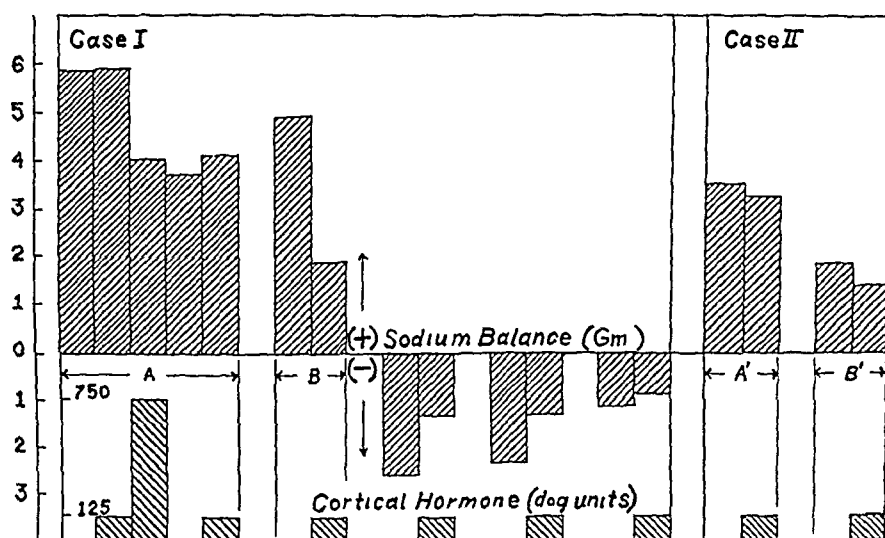


Chart 2—Chart indicating that sodium storage was not increased by adrenal cortical extract when there was adequate sodium intake, whereas excretion of sodium was diminished when the intake of sodium was low.

retention resulted from correction of sodium depletion rather than from use of the extract.

Sevringhaus¹⁰ stated that an oral preparation of cortical extract, "cortilex," is sufficiently active for therapeutic use. It was necessary, however, to ascertain whether this preparation was effective in our patients before we would recommend such therapy. Both patients were given eight tablets daily for three days. The first patient was in negative sodium balance, and a decrease of sodium excretion occurred, comparable to that obtained after administration of small doses of the parenteral extract. The other patient was storing sodium and showed no alteration

¹⁰ Sevringhaus, E. L. *Endocrine Therapy in General Practice*, Chicago, The Year Book Publishers, Inc., 1938.

in sodium excretion. A previous period during sodium storage in this patient also showed no effect following hypodermic administration of the extract.

Hartman and his associates⁹ reported that administration of cortical extract to a normal man resulted in a greater urinary excretion of potassium. Our data show no consistent alterations of urinary excretion of potassium following administration of cortical extracts.

Effect of Added Potassium—Wilder and his co-workers³ have previously shown that the addition of extra potassium intake will alter the course of Addison's disease and produce symptoms of crisis. Our

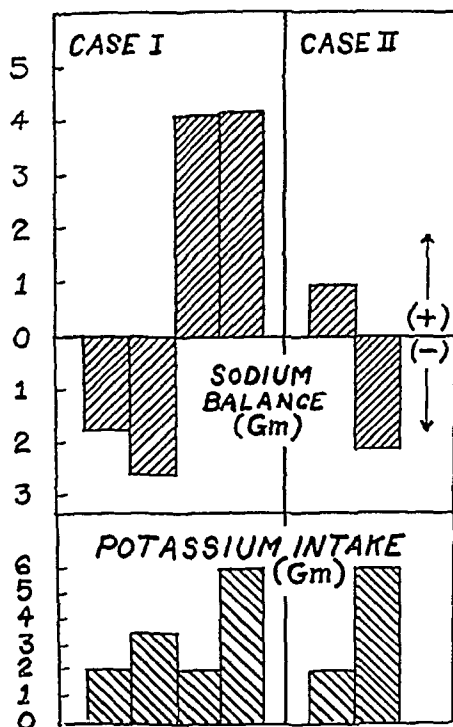


Chart 3—Chart indicating that excretion of sodium was not necessarily increased after administration of extra potassium. Manifestations of crisis, however, occurred

observations confirm theirs but differ in certain respects. Sodium depletion and storage appear to have a definite influence on the sensitiveness of our patients to the addition of potassium. They were less sensitive to potassium during periods of sodium storage and saturation than during periods of sodium loss and depletion. It is to be noted from chart 3 that addition of 1.45 Gm of extra potassium daily for three days resulted in acceleration of sodium excretion and that definite manifestations of crisis occurred, whereas during storage of sodium 4 Gm extra of potassium daily failed to alter sodium excretion but did produce a crisis. Furthermore, the addition of 1 Gm of extra potassium daily for seven days after sodium depletion had been corrected

did not produce a crisis in this patient. In our second patient, after correction of sodium depletion (chart 3) the addition of 4 Gm of extra potassium daily for two days was followed by a greater urinary excretion of sodium and symptoms of crisis.

It is of interest that manifestations of crisis appeared in our patients after the addition of extra potassium intake with or without an increase of sodium excretion.

Crisis—The theory that sodium loss is an important factor in the production of crisis is not substantiated by our observations. It does not appear that sodium storage or depletion alone will produce crisis. One of our patients had several attacks of crisis during a period when he was storing large amounts of sodium, but he did not have a crisis during another period of sodium storage or during a period of sodium depletion, although he went for fifty-four days in negative sodium balance and received no cortical extract for forty-four days. During this time the sodium content of the blood serum declined from 317 to 272 mg per hundred cubic centimeters. Furthermore, the administration of excess potassium produced manifestations of crisis regardless of whether the sodium excretion was increased and of whether the patient was storing or was losing sodium or sodium depletion had been eradicated. Sodium, however, apparently plays a role in the production of crisis. The patients appear to be more sensitive to potassium during depletion of sodium than they are if such depletion is corrected. It is possible also that sodium depletion plays a role in the production of the circulatory collapse which occurs in certain attacks of crisis. One of our patients had orthostatic hypotension during a period of sodium depletion, and such manifestations were eradicated after storage of sodium.

Potassium, on the other hand, appears to play an important role in the production of crisis, but the mechanism by which it produces a crisis is not clear. Entire white rats were analyzed during adrenal cortical insufficiency by Harrison and Darrow,¹¹ who found a definite increase in the potassium content of the entire animal. It was thought that changes of potassium content of the muscles probably accounted for the changes in the animals as a whole. It is difficult to attribute the production of crisis to a storage of potassium alone. Both of our patients stored potassium simultaneously with sodium without manifestations of crisis. Furthermore, crisis did not develop in our patients until from one to three days after extra potassium had been omitted, and patients appear to tolerate more potassium after correction of sodium depletion than during such depletion. These observations appear to support the contention that crisis develops because of disturbance in distribution.

11 Harrison, H. E., and Darrow, D. C. The Distribution of Body Water and Electrolytes in Adrenal Insufficiency, *J. Clin. Investigation* **17** 77-86, 1938.

of body electrolytes rather than that excess potassium produces a specific toxic effect

Chlorides—It is generally agreed that excretion of sodium is greater than that of chlorides in cases of adrenal cortical insufficiency and that chloride metabolism closely parallels that of sodium. Our results are in accord with this accepted idea except in one respect. It is to be noted from chart 4 that there was a greater urinary excretion of chlorides (milliequivalents) than of sodium (milliequivalents) in our first patient during the first twelve days of the initial period of sodium storage and that the two were approximately equal for the next twenty-eight days, or until a few days after sodium balance had been established. The excretion of sodium, however, exceeded that of chlorides (milliequivalents) during the remainder of the studies. This observation

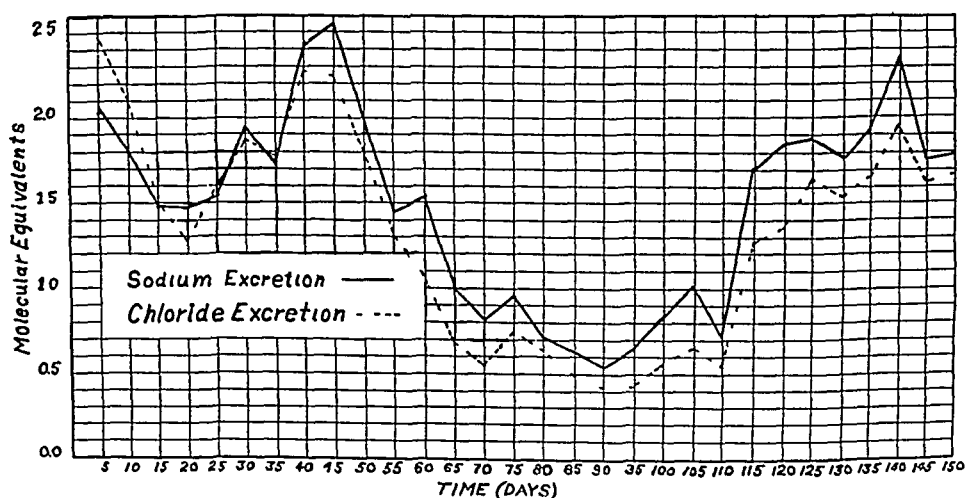


Chart 4—Relative excretion of sodium and of chloride. The latter exceeded the former for the first fifteen days, and the two were approximately equal for the next twenty days. The excretion of sodium exceeded that of chloride throughout the remainder of the study.

indicates that in certain instances there is a greater loss of sodium than of chlorides from the body and that the patients will store more milliequivalents of sodium than of chloride during a period of high sodium chloride intake. The urinary chlorides will be thereby greater than the urinary sodium on the basis of milliequivalents until sodium balance is established.

Observations Through an Infection and Until Death—Studies of sodium, potassium and chloride excretion during severe acute infections and until death in cases of Addison's disease have not been reported previously. One of our patients contracted a severe acute streptococcic infection of the upper respiratory tract and bronchopneumonia while our

studies were in progress. The patient had apparently recovered from the infection, with a return of temperature, pulse and respiration to normal for approximately thirty-six hours, when she suddenly became cyanotic, twitching of the face and extremities developed and she died. The arterial pressures had remained between 100 and 120 systolic, and the heart sounds were of good quality. It is to be noted from the accompanying table that there were no remarkable changes in excretion of electrolytes during the period of infection and none to account for sudden death.

Intake and Output of Sodium, Potassium and Chlorides in Relation to Administration of Adrenal Cortical Extract

	Sodium		Potassium		Chlorides		Adrenal Cortical Extract, Dog Units
	Intake, Gm	Output, Gm	Intake, Gm	Output, Gm	Intake, Gm	Output, Gm	
5/20/39	12 58	11 53	2 00	1 25	15 77	12 95	
5/21/39	12 58	12 20	2 00	1 38	15 77	15 90	
5/22/39	12 58	10 95	2 00	1 53	15 77	14 90	
5/23/39	9 20*	8 45		1 63	13 10	10 24	250
5/24/39	13 55	8 70	0 23	1 30	13 30	7 95	1,250
5/25/39	14 36	8 72	0 46	0 98	9 17	6 14	1,250
5/26/39	17 90	13 00	0 46	1 41	14 62	8 30	500
5/27/39	20 00	10 90	0 46	1 11	17 92	9 35	1,000
5/28/39	12 70	7 55	1 00	0 82	19 70	10 45	1,000
5/29/39	12 80	10 47	1 00	0 79	15 90	16 45	750

* Infection began

The table shows no significant changes in electrolyte balance during a severe infection and none to account for sudden death at 6 a. m. on May 30.

SUMMARY

The sodium, potassium and chloride excretion of 2 patients with previously untreated Addison's disease was studied.

A depletion of sodium was observed in both patients, and such depletion should be corrected. After it is corrected the patient ceases to store sodium. The rate of sodium storage during high sodium intake and a low constant potassium intake is not increased by therapeutic doses of cortical hormone. The rate of sodium loss, however, is decreased during negative sodium balance by cortical extract. Changes in body weight are a good criterion of sodium storage or loss provided the diet is constant and adequate. The addition of excess potassium will produce crisis regardless of whether sodium excretion is increased and patients appear to be more sensitive to potassium during sodium depletion than during sodium storage or saturation. Certain patients will deplete the body of more sodium than chloride, and the urinary excretion of chloride will be greater than that of sodium during a high sodium chloride intake. The causes of crisis are discussed, and the electrolyte excretion of a patient during a severe infection and until death is reported.

ANATOMIC FOUNDATION OF ANACIDITY

A GASTROSCOPIC STUDY

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INTRODUCTION

Anacidity has been considered one of the most important disturbances of the gastric function and often has been treated in textbooks as a separate disease¹ It has become customary to consider anacidity as either "functional" or "organic"

I FUNCTIONAL ANACIDITY

Several theories have been advanced to explain the failure of anatomically normal cells to secrete acid

1 *Psychogenic Influences*—It was believed that in patients with anacidity the cells themselves were able to produce acid but that they did not do so because a psychogenic barrier was established between the central nervous system and the end organs Such a condition would be similar to certain other psychogenic disturbances In hysterical paralysis, for instance, the paralyzed muscle has the potential faculty to contract but cannot contract because of psychogenic inhibition Certain authors have presented evidence to prove the psychogenic origin of anacidity Pavlov,² Bickel³ and others have demonstrated in experi-

From the Department of Medicine, University of Chicago

1 Compare for the following discussion A L Bloomfield and W S Pollard's outstanding monograph, *Gastric Anacidity Its Relation to Disease*, New York, The Macmillan Company, 1935

2 Pavlov, I P (a) *The Work of the Digestive Glands*, translated by W H Thompson, London, C G Griffin & Co, 1902, (b) *Conditioned Reflexes An Investigation of the Physiological Activity of the Cerebral Cortex*, New York, Oxford University Press, 1927

3 Bickel, A Experimentelle Untersuchungen uber die Einfluss von Affekten auf die Magensaftsekretion, *Deutsche med Wchnschr* 31 1829, 1905

ments on animals that psychic stimuli influence the gastric secretion. For a long time it was not believed that their conclusions could be applied to man. It had been forgotten how beautifully Beaumont⁴ had observed and described the influence of emotions on the gastric secretion a hundred years ago. However, Heyer⁵ later proved by hypnotic experiments that mental conditions may affect the gastric secretion. He made fractional analyses on patients in deep hypnosis and found that suggestion of all kinds of emotions, disagreeable ones (fear and emotions caused by pain, a feeling of danger of life and other experiences) as well as agreeable ones (taking a walk in the spring, winning in a lottery, recovering from sickness) stopped the flow of gastric juice, the former somewhat more quickly than the latter ones. Heilig and Hoff,⁶ using a similar technic, found that suggestion of food eaten with disgust may cause complete anacidity. Crucial experiments were carried out by Wittkower.⁷ After testing his subjects by repeated fractional analyses he suggested to them different emotions and maintained the effect for two hours, in the observations on 2 people he found not only that anacidity occurred after suggestions of disagreeable emotions but even that the anacidity was not influenced by the injection of histamine (1 cc of a 1:1,000 solution). A priori, this important observation of psychogenic inhibition of the secretion of histamine may seem difficult to accept, but it was corroborated later by Henning.⁸

2 *Constitutional Hereditary Debility of the Gastric Glands* (Martius⁹)—This theory was advanced especially by Hurst¹⁰ and his school. It was believed that for hereditary reasons the gastric glands were not able from birth on to secrete hydrochloric acid and that such a con-

4 Beaumont, W. Experiments and Observations on the Gastric Juice and the Physiology of Digestion, Plattsburgh, N. Y., F. P. Allan, 1833.

5 Heyer, G. R. Die Magensekretion beim Menschen unter besonderer Berücksichtigung der psychischen Einflüsse, Arch. f. Verdauungskr. **27** 227, 1921, **29** 11, 1921.

6 Heilig, R., and Hoff, H. Beiträge zur hypnotischen Beeinflussung der Magenfunktion, Med. Klin. **21** 162, 1925.

7 Wittkower, E. Über affektiv-somatische Veränderungen zur affektiven Beeinflussbarkeit der Magensekretion, Klin. Wchnschr. **10** 1811-1813 (Sept. 26) 1931.

8 Henning, N. Entzündung des Magens, Leipzig, Johann Ambrosius Barth, 1934.

9 Martius, F. Achylia gastrica und perniziöse Anämie, Med. Klin. **12** 481, 1916.

10 (a) Hurst, A. F. The Constitutional Factor in Disease, Brit. M. J. **1** 823, 1927, (b) Schorstein. Lecture on Precursors of Carcinoma of the Stomach, Lancet **2** 1023, 1929, (c) Observation and Experiment and Physiology of the Stomach, *ibid.* **2** 949, 1937.

dition may even have no pathologic significance. Many gastric analyses made on infants during the first months of life, especially before the development of any gastrointestinal troubles, did not give any evidence of such an inborn anacidity (Stewart¹¹). In a frequently quoted paper Bennet and Ryle¹² described their observations on 100 young, healthy students. In 4 of these students they found a complete anacidity, and the conclusion was drawn that a hereditary dysfunction of the acid-secreting cells must have been present. Faber¹³ recognized that this conclusion was not justified, for these students might have had symptomless chronic gastritis. Moreover, the possibility of a psychogenic anacidity in these patients could not be excluded. The demonstration of histamine-proved anacidity in the families of patients with pernicious anemia seemed to constitute further evidence of congenital anacidity. The conclusion appeared to be justified that this anacidity was a hereditary characteristic.

3 *Toxic Anacidity*—It was assumed that poisons or toxins were able to stop the function of the gastric glands. Anacidity from such a cause, if established, would scarcely be "functional." The fine organic structure of the acid-secreting cells might be damaged even though these changes could not be seen.

II ORGANIC ANACIDITY

In gastric carcinoma or gastric syphilis, the anacidity was assumed to be organic even though some of the mucosa appeared normal. An organic atrophy of the gastric mucosa was assumed to be the foundation of the anacidity always present in pernicious anemia. Faber and Lange¹⁴ rediscovered microscopically the chronic gastritis associated with gastric atrophy described earlier by Fenwick¹⁵ and others. Faber said that he considered chronic gastritis to be the only cause of anacidity, but the entity "chronic gastritis" was not generally accepted before the

11 Stewart, A. Gastric Acidity in Infants and Young Children Under Normal and Pathological Conditions, with Special Reference to Nutritional Anemia, *Brit J Child Dis* **34** 1, 1937.

12 Bennet, T. L., and Ryle, J. A. A Study of Normal Gastric Function Based on the Investigation of One Hundred Healthy Men, *Guy's Hosp Rep* **71** 286, 1921.

13 Faber, K. Gastritis and Its Consequences, London, Oxford University Press, 1935.

14 Faber, K., and Lange, G. D. Pathogenese und Aetiologie der chronischen Achylia gastrica, *Ztschr f klin Med* **66** 53, 1908.

15 Fenwick, S. On Atrophy of the Stomach and on the Nervous Affections of the Digestive Organs, London, J. & A. Churchill, 1880.

advent of gastrosocopy Today chronic gastritis is recognized as the most frequent gastric disease ¹⁶

GASTROSCOPIC STUDIES ON HISTAMINE-PROVED ANACIDITY

Gastrosocopy permits one to study the finer details of the gastric mucosa and thus to observe the changes associated with anacidity Henning and Jurgens ¹⁷ reported a study of 29 patients with achlorhydria after injection of histamine and found atrophy of the mucosa in 4 and severe gastritis in 13 of them McNeer and Barowsky ^{16b} found that different forms of gastritis may be present in patients with achylia Gaither and Borland ¹⁸ in their recent report stressed that they had seen "atrophy with achylia, achylia without atrophy and atrophy with normal gastric juice" A still more recent gastroscopic study made by K Luhr and M Sulzow ¹⁹ on pernicious anemia indicates that even in persons with this type of disease, the gastritis is not necessarily atrophic

We have analyzed the cases of 120 patients in whom at some time histamine-proved anacidity was found and on whom at about the same time a gastroscopic examination was performed ²⁰ Sixty-eight of these patients had only one histamine test and gastroscopic examination respectively, on 52 patients, a total of 428 histamine tests and of 349 gastroscopic examinations were carried out Thus, in the latter group each patient had an average of approximately 8.2 histamine tests and approximately 6.7 examinations by means of the gastroscope One patient had 61 histamine tests and another 41 gastroscopic examinations

This material may be divided for analytic purposes into three groups (1) patients with spontaneous anacidity in whom the gastric mucosa

16 (a) Katsch, G. Erkrankungen des Magens, in von Bergmann, G., and Staehelin, R. Handbuch der inneren Medizin, ed 2, Berlin, Julius Springer, 1926, vol 3, pt 1, p 553 (b) McNeer, G., and Barowsky, H. Gastroscopic Study of the Incidence of Chronic Gastritis in Common Gastric Afflictions, *Am J Digest Dis* **6** 181, 1939 (c) Schindler, R. Diagnostische Bedeutung der Gastroskopie, *Munchen med Wchnschr* **69** 535, 1922, (d) Gastrosocopy The Endoscopic Study of Gastric Pathology, Chicago, University of Chicago Press, 1937, (e) The Incidence of the Various Gastric Diseases as Revealed by Gastroscopic Study, *Am J M Sc* **197** 509, 1939

17 (a) Henning, N. Histaminprobe und endoskopisches Bilder Magenschleimhaut bei Achylie, *Munchen med Wchnschr* **76** 1561, 1929 (b) Henning, N., and Jurgens, R. Beziehungen der Farbstoffexkretion zur Sekretion und Morphologie der kranken Magens, *ibid* **77** 1961, 1930

18 Gaither, E. H., and Borland, J. L. Gastroscopic Studies, *J A M A* **110** 436 (Feb 5) 1938

19 Luhr, K., and Sulzow, M. Gastritisbefunde bei der Achylia perniciosa Gastroscopische Untersuchungen, *Deutsches Arch f klin Med* **182** 327, 1938

20 On all these patients the flexible Wolf-Schindler gastroscope was used, on most of them the so-called 50 degree model Of these patients, 98 were seen by us entirely, 1 was referred by Dr H Murphy, Buffalo, and 21 were referred by Dr L Berry, gastroenterologist at the Providence Hospital

as seen through the gastroscope looked perfectly normal, (2) those with spontaneous anacidity in whom the gastroscopic examination revealed an abnormal mucosa and (3) patients in whom the histamine-proved anacidity was produced artificially either (a) by operation or (b) by therapeutic roentgen irradiation

The first group presumably contains the patients with "functional" anacidity and consists of 5 members. The second group comprises the patients with anatomic changes producing, or combined with, anacidity, and consists of 96 persons. The last group, 19 patients in whom anacidity was produced artificially either by gastric operation or by therapeutic roentgen irradiation, may throw some light on the origin of postoperative anacidity and on the condition of the gastric mucosa after roentgen therapy.

I HISTAMINE-PROVED ANACIDITY ASSOCIATED WITH A NORMAL GASTRIC MUCOSA

In the total of 101 patients with spontaneous anacidity, only 5 per cent were found to have a perfectly normal gastric mucosa. This is perhaps the most important and the most surprising result of the analysis, especially if it is remembered that a normal gastric mucosa is found in 22.2 per cent of all patients on whom the gastroscope was employed.^{16e} Unfortunately it was not possible to watch any of these patients. Each of them was examined only once. Therefore, it cannot be stated (1) whether the gastric secretion was "capricious," anacidity frequently changing with acidity, (2) whether this anacidity was permanent or (3) whether perhaps later an organic disease of the stomach would have developed, the first stage of which could not be recognized gastroscopically. The possibility of a technical error can be excluded, it seems, for frequent checks have shown that the tip of the Rehfuß tube is almost invariably found in the most dependent part of the stomach. However, the position of the tube was not checked fluoroscopically in these 5 cases. The patients were not permitted to swallow their saliva.

Four of these patients were "nervous," but this finding certainly does not constitute valid evidence that the anacidity present was functional (Faber,¹³ Henning,⁸ Gutzeit,²¹ Schindler^{16d} and Bloomfield and Pollard¹). Satisfactory proof that secretion of histamine may be suppressed by psychogenic causes can best come, it seems to us, from studies made on patients in hypnosis. The fifth patient, a Negro, had had a general reaction to antisyphilitic therapy (bismuth) at the time of his examination, and it may be assumed that the anacidity in his case was toxic, probably with alteration of the finer structure of the gastric cells.

²¹ Gutzeit, K. Gastroskopie im Rahmen der klinischen Magendiagnostik, *Ergebn d inn Med u Kinderh* **35** 1, 1929

II SPONTANEOUS ANACIDITY ASSOCIATED WITH ORGANIC DISEASE OF THE GASTRIC MUCOSA

This group comprises 96 patients who will be considered in subdivisions having the following headings (1) lymphogranuloma, (2) diaphragmatic hernia, (3) uncomplicated chronic gastritis, (4) pernicious anemia and (5) gastric carcinoma

1 *Lymphogranuloma*—The report on 1 patient (case 6) with lymphogranuloma follows

A 48 year old man suffered from October 1936 from weakness. In March 1937 he began to have pain in the epigastrium, distention of the stomach, poor appetite and loss of weight. Four years before, he had roentgen therapy for microscopically proved Hodgkin's disease (lymphogranuloma).

At the time of admission there was generalized lymphadenopathy. The spleen and liver were palpable. A large mass was found in the epigastrium. By means of the histamine test anacidity was proved to be present on May 25, 1937. Roentgen examination revealed extreme thickening of the gastric mucosa, interpreted as infiltration with Hodgkin's tissue. At gastroscopic examination on June 2, 1937, big stiff folds and an undistensible stomach were the chief findings. The gastroscopic differential diagnosis between carcinomatous leather bottle stomach and other types of diffuse infiltrative lesions could not be made.

After roentgen therapy (2,652 roentgen units) the stomach became almost normal gastroscopically. The patient died at home July 12, 1937, and autopsy was not performed.

2 *Diaphragmatic Hernia*—The patient of case 7 had diaphragmatic hernia. Gastroscopically no inflammation was seen, but below the diaphragmatic ring there were two shallow noninflammatory ulcerations in the mucosa of the greater curvature. A histamine test was reported as giving a negative result. The course of this patient could not be followed.

3 *Uncomplicated Chronic Gastritis*—Usually (Faber,¹³ Schindler^{16d} and others), diffuse chronic nonspecific inflammation of the stomach is classified as superficial, atrophic or hypertrophic gastritis. Although superficial and atrophic gastritis present different histologic pictures, they belong to the same entity, for atrophic gastritis frequently develops from superficial gastritis. Hypertrophic gastritis probably is a distinct entity, although there are a few cases in which gastroscopic examination reveals the picture of hypertrophic nodes while microscopic examination reveals atrophy associated with compensatory hyperplasia. However, with some experience this form may be suspected at gastroscopic examinations, and we have classified the only example of this kind of gastritis occurring in our series under the heading atrophic gastritis. There are some cases of swelling of the gastric mucosa together with formation of superficial ulcerations in which it is difficult to determine whether the inflammation is superficial or hypertrophic. When observed long enough these conditions usually are seen to belong to the hyper-

trophic group Among the 55 patients with uncomplicated gastritis the distribution according to types of the disease was as follows

Type of Gastritis	No of Patients
Hypertrophic	6
Superficial	12
Atrophic	37
Superficial plus atrophic	7
Pure atrophic	30

This observation corresponds approximately with Henning's findings. The occurrence of anacidity in persons with superficial and hypertrophic gastritis was not expected, for the glandular apparatus was presumably intact. It seems likely that the functioning cellular structures may be damaged by the inflammatory process, often perhaps in only a mild

TABLE 1—*Transient Anacidity in a Patient with Severe Chronic Hypertrophic Ulcerative Gastritis (Case 12)*

Date	Result of Histamine Test	Report on Gastroscopic Examination
11/18/37	22	
12/13/37		Erosive superficial (?) gastritis
2/7/38	0	
2/21/38		Chronic hypertrophic ulcerative gastritis
3/10/38	40	
3/14/38		Unusually severe chronic hypertrophic ulcerative gastritis
7/14/38	70	
7/20/38		Ulcerative gastritis, the picture has become worse
8/17/38	12	All portions of the stomach look normal except small area of upper part of lesser curvature, in which the mucosa appears velvety
9/21/38	22	
9/28/38		Recurrence of severe hypertrophic ulcerative gastritis
10/19/38	41	
10/26/38		Severe hypertrophic ulcerative gastritis of the body

transitory manner, as will be shown later, in the study of histamine-proved anacidity produced by roentgen irradiation.

(a) Hypertrophic Gastritis It should be noted that in no patient with hypertrophic gastritis was the presence of permanent anacidity proved. Among 4 of the 6 patients (cases, 8, 9, 10 and 11) in this group, there was only one histamine test. The gastritis was of the simple hypertrophic type, located chiefly in the body of the stomach in 3 patients and in the antrum in 1. Two patients (cases 12 and 13) were observed over a long period. The first (case 12) was a 37 year old man, who complained of dull pain in the epigastrium for twenty years and a tired feeling for three years, together with lack of appetite. He had consumed 4 to 6 ounces (120 to 180 cc) of whisky every night for many years. At roentgen examination no ulcer was found. The findings of the histamine tests and gastroscopic examinations of this patient are listed in table 1.

This case shows that histamine-proved anacidity is not correlated with the apparent seriousness of the inflammation, furthermore, that

"capricious" behavior of the acid secretion does not prove functional or psychogenic anacidity but may exist in the presence of severe and striking organic changes. This capricious behavior was even more pronounced in a patient (case 13) with gastric ulcer in whom there were unusually severe hypertrophic gastritis and transitory anacidity, shown in table 2.

The inflammation at the first of 5 gastroscopic examinations (May 25, 1938) appeared extremely severe, causing unusual thickening and infiltration, so that even the presence of a malignant infiltration instead of a benign ulcer with surrounding inflammation was considered.

TABLE 2—"Capricious" Behavior of Anacidity Transient Anacidity in a Patient Having Ulcer Associated with Unusually Severe Hypertrophic Gastritis (Case 13)

Date	Result of Histamine Test	Report on Gastroscopic Examination
5/25/38		Ulcer at angulus with unusual thickening and stiffness of the mucosa of the antrum and posterior wall
5/28/38	60	
6/ 1/38	30	
6/ 4/38	30	
6/ 8/38	5	
6/13/38		Previously seen hypertrophic gastritis has subsided to a great extent, two shallow ulcerations with hemorrhagic halos
6/15/38	0	
6/16/38	10	
6/27/38	0	
7/27/38		Ulcer scar
8/15/38	42	
10/ 8/38	62	
10/15/38	0	
10/19/38		Recurrence of benign ulcer, severe hypertrophic gastritis of lesser curvature
10/29/38	78	
11/ 9/38	80	
11/12/38		Ulcer healed
11/19/38	0	
1/ 6/39	62	

(b) Superficial Gastritis. There were 12 patients (cases 14 through 25) whose condition was classified as superficial gastritis. In 8 of them (cases 15 through 22) superficial gastritis of the body of the stomach was seen, in 1 patient combined with shallow erosions. Although sometimes superficial isolated antrum gastritis may be observed, such a condition was not found in our series. In 3 patients the superficial gastritis was localized, being present in the first of these only in the lower portion of the lesser curvature of the body (case 22), in the second only in the upper portion of the greater curvature (case 23) and in the third in the anterior wall of the body (case 24). In 1 patient (case 25) superficial gastritis of the posterior wall was found together with two small benign tumors (polyps). Polyps usually develop in an inflamed mucosa, but atrophic gastritis is found much more frequently than superficial gastritis. The histamine-proved anacidity seems more likely to be related to the gastritis than to the polyps.

(c) Superficial Gastritis Transformed into Atrophic Gastritis Seven patients (cases 26 through 32) had superficial gastritis which became atrophic gastritis. In those patients in whom the transition can be observed directly by gastroscopic examinations, the atrophic changes are usually found to start in the upper portions of the stomach. In 2 of our patients (cases 26 and 27) superficial gastritis was found in the antrum and atrophic gastritis in the body. In 3 (cases 28, 29 and 30) superficial gastritis was present in the lower portions of the body and atrophic in the upper portions. In only 1 patient (case 31) atrophic gastritis was found at the anterior wall of the body and superficial changes were found in the fornix.

The case of the last patient in this group is unusual (case 32), for a huge gastric ulcer preceded the development of anacidity and of superficial and atrophic gastritis (Palmer and Nutter²²). A brief summary of this case follows.

Between Jan 6, 1937 and April 24, 1939 the patient had twenty-three gastroscopic examinations, twenty-eight histamine tests and eighteen roentgen examinations. In the beginning a large benign ulcer of the midportion of the anterior wall near the lesser curvature was found, surrounded by hypertrophic gastritis. The ulcer had healed on April 7, 1937. On Jan 5, 1938 we thought we saw atrophy of the mucosa for the first time. This was not confirmed at later observations. The degree of the gastric acidity, however, which had been up to 75 clinical units in the beginning, was at that time only 10 and remained rather low during the next year. On March 3, 1939 again a shallow benign ulcer was seen, this time in the lower part of the lesser curvature and accompanied by extensive superficial gastritis with one patch of atrophy. The ulcer healed rapidly, but from this date on patches of atrophic gastritis were observed continuously together with superficial gastritis. The value for acidity was only 5 on Feb 28, 1939, histamine-proved anacidity was found on March 4, March 10, March 20 and April 5, 1939. On April 19 and April 21, 1939 acid was present in values of 10 and 35 clinical units. At the time hypertrophic gastritis was found, acid was present, which decreased when the hypertrophic gastritis and the ulcer healed. Severe superficial and atrophic gastritis were observed when the acid disappeared completely. Although the gastroscopic picture remained unchanged, absence and presence of acid interchanged again in the most capricious manner.

Schiff,²³ in his analysis of the case of 1 patient observed over years, found that the human stomach may temporarily lose, or exhibit a marked decrease in, its ability to secrete free hydrochloric acid. In his patient there was mild superficial gastritis without any demonstrable change in the severity of the gastritis when histamine-proved anacidity occurred.

(d) Atrophic Gastritis This group (cases 33 through 59) comprises 30 patients, but 3 of them are discussed under a separate heading (e) because they were in the families of patients with pernicious anemia.

22 Palmer, W. L., and Nutter, P. B. Gastric Ulcer and Achlorhydria, *Arch Int Med* 65:499 (March) 1940.

23 Schiff, L. Gastric Secretion in Man, *Arch Int Med* 61:774 (May) 1938.

When these 30 patients are studied in combination with the 7 in the previous group, it becomes evident that macroscopically visible atrophic changes are the most frequent organic inflammatory disease found to accompany anacidity. The usual statistical relation between hypertrophic, superficial and atrophic gastritis is in the ratio 14 12 19, whereas among these 55 persons it was 6 12 37, thus indicating that the correlation between anacidity and atrophic gastritis is much closer than that between anacidity and superficial or hypertrophic gastritis.

Extensive atrophic gastritis of the entire stomach or of almost the entire stomach, including both antrum and body, was present in 17 of the 27 patients. A diffuse atrophy involving either the entire body of the stomach (3 patients) or only the upper portion (3 patients) but not the antrum was found in 6 patients. No person was found in this series in whom the antrum alone was atrophic. In the 4 remaining patients the atrophy was patchy, involving both the antrum and the body in 2 patients and in 2 others the body alone. In 1 patient with complete atrophy (case 33) a benign polyp was found. In another (case 34) the atrophic mucosa became normal gastroscopically after iron therapy (Schindler, Kirsner and Palmer²⁴) but the reaction to the histamine test remained negative. Unfortunately, further gastroscopic studies could not be made. The case of another patient (case 35), the course of whose disease was exceptionally well observed, is being reported in detail in another publication,²⁴ but the data pertinent to the present paper may be summarized as shown in table 3.

Although the acid curve in this case may have been influenced by the therapy, the "capricious" behavior of the acid secretion, formerly considered characteristic of "nervous" anacidity, was found here before and after therapy and in association with severe organic changes. The case of 1 of the patients with patchy atrophic gastritis is important because the condition was tropical sprue (Rodriguez-Olleros²⁵). The gastroscopic observations, the blood findings and the results of histamine tests are listed in table 4.

Liver therapy (intramuscular injections of the Lederle concentrate, 1 cc) was instituted on Oct 18, 1934. Although the acid gastric secretion had returned by May 13, 1935, the atrophic changes of the gastric mucosa were more extensive at this time than before and were found to have improved spectacularly only on April 28, 1937.

(e) Anacidity in Relatives of Patients with Pernicious Anemia. Three patients (cases 6, 61 and 62) comprised this group. The occurrence of histamine-proved anacidity in relatives of patients suffering

24 Schindler, R., Kirsner, J. B., and Palmer, W. L. Atrophic Gastritis. Gastroscopic Studies on the Effect of Liver and Iron Therapy, *Arch Int Med* 65:78 (Jan) 1940.

25 Rodriguez-Olleros, A. The Stomach in Tropical Sprue, Puerto Rico J Pub Health & Trop Med 13:503, 1938.

TABLE 3—"Capricious" Behavior of the Acid Curve of a Patient with Severe Atrophic Hyperplastic Gastritis (Case 35)

Date	Result of Histamine Test	Report on Gastroscopic Examination
6/13/38	0	
6/20/38		Severe hypertrophic ulcerative gastritis of the entire stomach
7/11/38		Hypertrophic gastritis of the body much improved
7/21/38	35	
7/25/38		Rapidly progressive hyperplastic atrophic gastritis
8/ 1/38		Atrophy had developed, extensive
8/10/38		Patchy atrophic gastritis in the lesser curvature and fornix
8/12/38	30	
8/17/38		Extensive patchy atrophic hemorrhagic gastritis
8/31/38		Extensive atrophic gastritis
9/ 3/38	0	
9/ 8/38		Extensive atrophic gastritis
9/16/38		Extensive atrophic gastritis
9/18/38	0	
9/26/38		Sudden development of severe superficial gastritis after treatment with nicotinic acid
10/ 3/38	20	
10/12/38		Disappearance of superficial changes, atrophy in the midportion of the stomach
10/28/38	30	
10/31/38		Extensive atrophic gastritis
11/14/38		Extensive atrophic gastritis
2/ 1/39		Spectacular improvement of atrophic gastritis after vitamin therapy
3/ 8/39	14	
3/ 9/39		Again atrophy involving practically the whole stomach
4/10/39		Atrophic gastritis much improved (vitamin therapy)
4/17/39	41	
4/24/39		Still some atrophic gastritis of the lesser curvature

TABLE 4—Acid Reappearing in a Patient with Tropical Spine (Case 59)

Date	Blood Count			Acid	Gastroscopic Findings
	White Blood Cells	Red Blood Cells	Hemoglobin		
10/ 8/34	3,500	1 80	50%		
10/ 9/34				Ewald "0"	
10/10/34				Histamine 0	
11/ 1/34					Small patches of atrophic gastritis of the anterior wall of the body
12/21/34	6,500	3 91	78%		
5/13/35				Histamine 60	
5/17/35	8,300	4 56	81%		
5/25/35	-				Atrophic gastritis has become more extensive, involving the upper portions of the stomach more severely
4/13/37	12,400	4 73	85%		
4/14/37				Histamine 50	
4/28/37					Atrophic gastritis spectacularly improved only in the lower portions of the stomach slight swelling of the upper portions
6/29/38	10,200	4 33	86%		
7/ 6/38				Histamine 100	
7/ 8/38					Only one small patch of atrophic gastritis of the anterior wall
7/11/38	8,300	3 67	72%		
12/ 9/38		4 32	87%		
10/ 3/39	11 200	4 20	75%		

from pernicious anemia has been mentioned as evidence in support of the theory of the constitutional, or inborn, character of anacidity. This point seemed to us to be so important that we sought definite confirmation. Two members of families in which pernicious anemia occurred were examined by us, and a third was studied by Dr H. Murphy in Buffalo. We naturally expected to find a perfectly normal gastric mucosa and were surprised to see severe inflammatory atrophic changes in the stomach of each of these 3 patients. A brief account of their cases follows.

CASE 60 (examination by Dr. Murphy) —The mother of this 44 year old woman died of pernicious anemia, one brother has pernicious anemia, and the patient herself has had for ten years considerable bloating after meals, nausea and faintness somewhat relieved by food, lack of energy and a poor appetite. Results of the physical examination were normal. Determination of the blood count showed a hemoglobin value of 83 per cent, red blood cells numbering 4,400,000 and 9,950 white blood cells. The smear was normal. Examination by means of the gastroscope revealed marked atrophic gastritis involving the entire body of the stomach.

CASE 61 —A 37 year old woman complained of stomach disorders and a tired feeling for ten years. Her father had died of pernicious anemia. Anacidity had been found first eight years before our examination, confirmed by several rechecks in the following years. Histamine-proved anacidity was found on March 4, 1939. Gastroscopic examination, done on March 3, 1939, revealed severe atrophic hemorrhagic gastritis involving the entire stomach.

CASE 62 —A 59 year old woman was admitted to the clinic because of edema of the right arm following radical mastectomy and was examined by us because a sister had been in our institution for treatment of pernicious anemia. The hemoglobin value was 78 per cent, the red blood cells numbered 4,380,000 and the white blood cells 6,200. Histamine-proved anacidity was found on March 18, 1935. Gastroscopic examination on March 23, 1935 revealed patchy atrophic gastritis of the body of the stomach.

Thus, in 3 relatives of patients suffering from pernicious anemia severe atrophic gastritis was found, together with histamine-proved anacidity.

4 *Anacidity in Persons with Pernicious Anemia* —This group consisted of 16 patients (cases 63 through 78). The conditions of most of these patients have been described in a previous paper (Schindler and Serby²⁶). The added cases do not bring out new facts. The anatomic features presented by this group of patients, therefore, may be described briefly. All untreated patients have, rarely, either superficial gastritis or superficial gastritis plus atrophic gastritis, or, as a rule, either patchy or diffuse atrophy. This atrophy should be considered an inflammatory process. Gastroscopic differentiation cannot be made between the atrophic gastritis seen in patients with pernicious anemia

26 Schindler, R, and Serby, A. M. Gastroscopic Observations in Pernicious Anemia, Arch Int Med 63 334 (Feb) 1939

and that seen in those with other types of anemia or in persons without anemia. After sufficient treatment there may be either no improvement of the condition of the gastric mucosa or even definite progression of the atrophy, or there may be found definite improvement, even to the point of a gastroscopically normal mucosa. No histologic study has been done in the latter cases, and it remains to be seen whether this apparent regeneration is a true regeneration in the histologic sense. In our series there was no patient in whom the hydrochloric acid reappeared, even after the gastric mucosa had become apparently normal.

The anacidity of pernicious anemia remains difficult to explain satisfactorily. If it were due to the anemia per se it should disappear as the anemia disappears, but it does not do so. If it were simply a result of the gastritis the acid secretion should return as the mucosa becomes apparently normal, unless it is assumed that the injury is too slight to be visible grossly. It is possible that the secretion of hydrochloric acid is inhibited by some type of damage to the cells not visible gastroscopically or microscopically and independent of the gastritis. The theory that the anomaly is hereditary is not supported by the studies of the patients in families with pernicious anemia, for in all of these 3 patients severe gastritis was found. The cases of these patients also indicate that the gastritis does not result from the anemia.

5 *Anacidity in Persons with Malignant Gastric Tumors*—In this group were 23 patients (cases 79 through 101). It is well known that malignant gastric tumors are accompanied by anacidity in about 60 per cent of all cases, but the cause is still not known. The anacidity has been assumed to be secondary to the tumor and due to toxic products of decay, but strong evidence has been brought forward that many or all gastric carcinomas develop on the soil of atrophic gastritis and that the anacidity usually precedes the development of the tumor (Saltzmann,²⁷ Konjetzny,²⁸ Faber,¹³ Hurst,^{10c} Schindler,²⁹ Bloomfield and Pollard¹ and Schindler and Gold³⁰). Brunschwig³¹ has recently observed that intravenous injection of anacid gastric juices from cancerous stomachs into dogs with subtotal gastric pouches produces a transitory anacidity in approximately 80 per cent of cases, as compared with approximately

27 Saltzmann, F. Studien über Magenkrebs mit besonderer Berücksichtigung der Schleimhautveränderungen, in *Arbeiten aus dem pathologischen Institut der Universität Helsingfors, Jena, Gustav Fischer, 1913, p. 355*.

28 Konjetzny, G. E. Ueber die Beziehungen der chronischen Gastritis mit ihren Folgeerscheinungen und des chronischen Magencarcinoms zur Entwicklung des Magenkrebses, *Beitr. z. klin. Chir.* **85** 455, 1913.

29 Schindler, R. Die Bedeutung der Gastroskopie für die Heilung des Magenkrebses, *Monatschr. f. Krebsbekämpfung* **1** 203, 1933.

30 Schindler, R., and Gold, R. Gastroscopy and Gastric Carcinoma, Especially in Its Early Diagnosis, *Surg., Gynec. & Obst.* **69** 1, 1939.

31 Brunschwig, A. A Secretory Depressant in Gastric Juice of Patients with Pernicious Anemia, *J. Clin. Investigation* **18** 415, 1939.

20 per cent positive results obtained in a control series of injections of juices from patients without carcinoma of the stomach or pernicious anemia, some of whom had histamine-proved anacidity. Furthermore, results similar to those obtained with antacid juices from cancerous stomachs were obtained when antacid juices from patients with proved pernicious anemia were used. This raises the question whether the anacidity accompanying cancer of the stomach and indeed pernicious anemia may not be the result of a secretory depressant of unknown origin.

Twenty-two of our patients had gastric carcinomas, 1 had a lymphoblastoma. In 10 patients with gastric carcinoma, associated atrophy of the gastric mucosa was found. There was evidence that in 2 of these 10 patients the atrophic gastritis had preceded the development of the gastric tumor. One of these 2 (case 79) had had severe stomach trouble and histamine-proved anacidity eight years prior to the development of the carcinoma. Gastroscopic examination disclosed the carcinoma and complete atrophy of the mucosa. The second patient (case 80, not included in the series of patients with pernicious anemia) was suffering from pernicious anemia and combined cord degeneration for several years, consequently atrophic gastritis had certainly been present, and incidentally a small carcinoma was found and verified by operation. In the case of 6 patients the sequence of events could not be established. In 3 patients (cases 81, 82 and 83) no definite gastritis was found by gastroscopic examination, in these 3 there was extensive ulceration of the tumor. In 8 patients the tumor was so enormous that good visualization of the noninfiltrated mucosa could not be obtained. In 1 patient remnants of barium prevented adequate study of the mucosa. In the 1 patient with lymphoblastoma no definite changes of the non-invaded gastric mucosa were found.

The conclusions from the study of this group of patients are: 1. Atrophic gastritis and anacidity may precede the formation of gastric cancer. 2. In many cases severe atrophic gastritis may be found to accompany gastric carcinoma and may be responsible for the anacidity. 3. There are, however, a few cases in which the mucosa grossly is normal. In these cases either gastroscopic examination fails to reveal fine atrophic changes, or the anacidity is due to toxins of the carcinoma inhibiting the action of the secreting cells or to a secretory depressant (Brunschwig³¹).

III ARTIFICIALLY PRODUCED ANACIDITY

Histamine-proved anacidity may be produced artificially in two different ways, either by surgical procedure or by roentgen irradiation. Both are done for therapeutic purposes. Our material contained 8 patients with postoperative anacidity (cases 102 through 109) and 11 with anacidity following roentgen irradiation of the stomach (case 110 through 120).

1 *Anacidity Following Gastric Surgical Procedure*—The 8 patients (cases 102 through 109) with postoperative anacidity will be discussed first. The purpose of gastric resection for ulcer was to eradicate the chronic ulcer and the ulcerous area of the stomach. The subsequent anacidity was not easy to understand, for the acid-secreting cells are located in the body of the stomach and even a large resection could not remove all of them. There are two theories to explain this kind of acidity, the first of which is as follows. The pyloric region has normally a stimulating influence on the acid-secreting glands, when this stimulus is missing no acid can be secreted. This theory has been disproved by the convincing experimental study of Portis and Portis,³² although European surgeons still recommend the so-called Madlener operation,³³ i. e., the resection of the pyloric antrum in cases of ulcer at the cardia, an operation based on the theory mentioned. The postoperative anatomic condition of the mucosa of the stomach has been disregarded, because the study of it was impossible before the gastroscopic era.

We observed 2 patients who had a gastroenterostomy and who suffered from histamine-proved anacidity. On the first patient the operation was performed in 1925 for duodenal ulcer (case 102). On May 3, 1936 the histamine test showed anacidity. Gastroscopic examination carried out on April 3, 1936 revealed severe gastritis of the edge of the stoma and of the lower portions of the body. On the second patient (case 103) the gastroenterostomy was performed in 1936 at Heidelberg for duodenal ulcer. At examination by means of the gastroscope on May 9, 1938, the stoma was found to be patent, and extensive superficial and atrophic gastritis was observed. In these patients the pyloric region was present, nevertheless, no acid was found. However, severe gastritis was revealed.

The occurrence of severe gastritis following a gastric operation will not surprise any one who has watched gastroscopically the stomach of a dog in which a gastric fistula had been made for a week or so, tremendous swelling and reddening of the gastric mucosa developed, subsiding only after many weeks. Gastroscopic observations have shown (Schindler,^{16c} Gutzeit,²¹ Henning,³⁴ Moutier,³⁵ Hertel and Kallius,³⁶

32 Portis, S. A., and Portis, B. Effects of Subtotal Gastrectomy on Gastric Secretion, *J. A. M. A.* **86** 836 (March 20) 1926.

33 Madlener, M. Ueber Pyloroktomie bei pylorusfernem Magengeschwür, *Zentralbl. f. Chir.* **50** 1313, 1923.

34 Henning, N. Ueber die Gastritis nach Magenoperationen, *Zentralbl. f. inn. Med.* **54** 49, 1933.

35 Moutier, F. Etude endoscopique de la gastroentérostomie, *Presse med.* **42** 653, 1934.

36 Hertel, E., and Kallius, H. U. Beiträge zur Gastroskopie des operierten Magens, *Arch. f. klin. Chir.* **151** 578, 1928.

Carey³⁷ and Schindler and Giere³⁸) that severe gastritis unfortunately is the most common postoperative disease of the stomach. Since chronic gastritis, as shown previously, is often the cause of anacidity, it seems likely that in cases of anacidity following gastroenterostomy gastritis may play an important role in the cessation of secretion.

Among our group of 6 patients with resected stomachs, 1 resection on 5 was carried out because of ulcer. On 1 of them (case 104) the gastroscope was used as soon as the sixteenth postoperative day, and acute tremendous gastritis was found, with the production of so much mucus and pus that no detail of the gastric mucosa could be made out, a picture similar to that observed postoperatively in the stomachs of dogs. The histamine test at the same time revealed absence of acid. This gastritis then became chronic and developed into total atrophy, the result of the histamine test always being negative. Immediately before the operation the value of acid had been up to 48 units. At gastroscopic examination before the operation, only inflammation around the ulcer had been found. This patient had had a total of 34 histamine tests and 32 gastroscopic examinations over a period of a year and a half. The severe acute gastritis absent before operation but found immediately after gastric resection and rapidly developing into atrophy may well have been responsible for the postoperative histamine-proved anacidity.

A second patient was equally well observed (case 105). He had had a gastroenterostomy in the fall of 1926. On Dec 5, 1934, the histamine test revealed an anacidity of 25 and gastroscopic examination a marginal ulcer but not gastritis. Resection was performed on Sept 12, 1934, and then, from Nov 28, 1934 on, severe gastritis developed, which later improved but never disappeared entirely. On one occasion the histamine test revealed an acidity value of 8, but otherwise the histamine tests showed absence of hydrochloric acid.

In the other 3 patients (cases 106, 107 and 108) on whom resection following ulcer was performed, histamine-proved anacidity was found together with severe gastritis. On the other hand, when we examined gastroscopically patients having normal acidity after resection, we sometimes found an entirely normal mucosa (Schindler and Giere³⁸).

The 1 patient (case 109) in whom anacidity was found after resection of a carcinoma will not be discussed because of the recurrent carcinoma present.

Thus the conclusion is reached that histamine-proved anacidity in stomachs on which gastroenterostomy has been done, with or without resection, may be found together with extremely severe gastritis, the

37 Carey, J. B. Gastroscopic Observations of the Postoperative Stomach, *Surg, Gynec & Obst* 65:447, 1937.

38 Schindler, R., and Giere, N. Gastric Surgery and Gastroscopy, *Arch Surg* 35:712 (Oct) 1937.

acute stage of which may be observed immediately after operation, later developing into extensive atrophy

2 Anacidity Following Roentgen Irradiation—This group, 11 patients (cases 110 through 120), will be reported on only briefly, because the material on it belongs to data published elsewhere (Palmer and Templeton³⁹) and because the anatomic changes resulting from this type of therapy will be considered more extensively later. The purpose of the therapy was the production of anacidity artificially by roentgen therapy in patients with ulcer, thus removing one of the causes essential for the formation of chronic gastroduodenal ulcer. In a number of these patients histamine-proved anacidity developed and remained for a period of days or months. On 10 of them gastroscopic observations were carried out at the time of the anacidity. On most of these several examinations were made, and only twice was a normal mucosa found. In the first of these patients (case 110) treatment with 1,758 roentgen units was given from June 26 to July 2, 1937 (the details appear in Palmer and Templeton's paper³⁹). Histamine-proved anacidity was found from Oct 8, 1937 to July 18, 1938, after this date the acid reappeared. Seven gastroscopic examinations were carried out within this period, and always superficial gastritis was found except at one examination, made on April 1, 1938. On this day a normal mucosa was found. Superficial gastritis was later observed even after the hydrochloric acid had come back. Therefore, it seems unlikely that organic changes should have been absent on this date. This observation seems to us important in demonstrating that at gastroscopic examination an apparently normal mucosa may rarely be seen when organic changes are certainly present. The assumption made earlier that chronic inflammation may alter a grossly normal mucosa to such an extent as to prevent secretion of acid seems to be supported by this observation. To the other patient (case 111) who had a gastroenterostomy treatment with 2,930 roentgen units was given from Feb 8 to 18, 1938. Histamine-proved anacidity was found only on March 10 and on March 24, 1938. Gastroscopic examinations on March 11, 1938, on July 25, 1938 and on April 7, 1939 revealed a normal mucosa. In this case the anacidity was of short duration, so that it is conceivable that the effect of the roentgen rays on the mucosa cells was sufficient to stop the secretion of acid for two weeks but not sufficient to produce macroscopic changes. Here again histamine-proved anacidity was present, certainly not due to psychogenic or nervous factors, perhaps complicated by the gastroenterostomy, but nevertheless without pathologic change being visible in the mucosa gastroscopically.

39 Palmer, W. L., and Templeton, F. The Effect of Radiation Therapy on Gastric Secretion, *J. A. M. A.* **112** 1429 (April 15) 1939.

In the other 8 patients an abnormal mucosa was found at gastroscopic examination as long as histamine-proved anacidity was present. The first finding, 21 days after roentgen therapy, was a reddening of the mucosa, the first sign of superficial gastritis (case 112). In 4 patients (cases 113 to 116) outspoken superficial gastritis was seen, usually disappearing when the acid reappeared. The histologic substrate of this gastritis apparently consists of severe inflammatory changes at the base of the necks of the glands and minor degenerative changes in both chief and parietal cells (Palmer and Templeton³⁹). In 2 patients, however (case 110, discussed in the first paragraph of this section on anacidity following roentgen irradiation, and case 117) the superficial gastritis outlasted the anacidity, finally turning into atrophic gastritis. In 2 other patients (cases 118 and 119) atrophic gastritis was present in the beginning and increased in severity.

To the last patient (case 120) roentgen therapy was given for another reason. At gastroscopic examination severe hyperplastic atrophic gastritis with many ulcerations had been seen. At that time normal acidity was found. A laparotomy was done and a specimen for biopsy taken from the gastric wall; microscope examination revealed a picture highly suggestive of lymphoblastoma. The glandular apparatus in this specimen was partly destroyed by lymphocytic invasion. (Illustrations of this case will be found in another publication,⁴⁰ fig 6.) Roentgen therapy (2,878 r) was given, after which histamine-proved anacidity developed, although the gastroscopic picture remained unchanged. This was probably "lymphoblastomic" atrophic gastritis. Evidently before the irradiation enough glands were left intact to produce acid, whereas the irradiation altered the structure of these cells so that they were unable to secrete acid any longer.

SUMMARY AND CONCLUSIONS

Gastroscopic examinations were made on 101 patients having spontaneous histamine-proved anacidity and on 19 patients having artificially produced anacidity. The results of the examinations were as follows:

1. Gross anatomic lesions were observed in all except 5 patients. Anatomic changes gastroscopically invisible had to be assumed in the case of 1 patient with chronic bismuth poisoning. In the remaining 4 patients psychogenic functional anacidity seemed possible but could not be proved.

2. In 55 patients diffuse inflammation was seen, 6 of them presenting the picture of hypertrophic gastritis, 12 that of superficial gastritis, 7 that of superficial gastritis with transition into atrophic

40 Schindler, R. Gastritis Simulating Tumor Formation, *Am J Digest Dis* 6: 523, 1939.

gastritis and 30 that of atrophic gastritis. These diffuse changes usually were located in the body of the stomach. It seems to us to be most likely that the anacidity is the result of an inflammatory process. The apparent extent and severity of the inflammatory process do not necessarily bear a constant relationship to the anacidity.

3 In 3 members of families in which pernicious anemia occurred, histamine-proved anacidity was found associated with severe atrophic gastritis. This observation deprives the theory of the inborn constitutional character of anacidity of its best support, for the anacidity may be attributed to the gastritis.

4 Of 16 patients having pernicious anemia together with anacidity, superficial gastritis or superficial plus atrophic gastritis was seen in 2. Atrophic gastritis (patchy or complete) was observed in 12 patients. The gastric mucosa appeared to be normal after liver therapy in only 2 of the 16 patients in this series.

5 The observations in 23 patients with malignant gastric tumor together with histamine-proved anacidity were in accord with the concept that atrophic gastritis plus anacidity may precede the formation of gastric carcinoma and that in many cases severe atrophic gastritis may be responsible for the anacidity, but in 3 patients examination by means of the gastroscope failed to reveal gross evidence of pathologic changes in the gastric mucosa itself.

6 Eight patients with anacidity following a gastric operation were observed, on 2 of them the operation having been gastroenterostomy and on 6 resection. All of them had severe diffuse gastritis. In 2 patients no diffuse gastritis and no anacidity was found before the operation, whereas after the operation severe purulent acute gastritis and later chronic gastritis with anacidity developed. It seems likely that the anacidity following gastric operation may be due not only to the reflux of intestinal content but also to postoperative gastritis.

7 In 11 patients having histamine-proved anacidity after roentgen irradiation, definite diffuse inflammatory changes were usually found, ranging from mild transient superficial to constant atrophic gastritis. However, at two observations an apparently normal gastric mucosa was seen. This proves that mild organic lesions of the gastric mucosa, producing anacidity, may be present without giving a pathologic picture gastroscopically.

INFLUENCE OF THIAMINE ON BLOOD SUGAR LEVELS IN DIABETIC PATIENTS

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In the past few years there has been considerable interest in the relationship between carbohydrate metabolism and vitamin B₁. As Williams and Spies¹ pointed out in their recent monograph "There is convincing evidence of frequent disturbances of glycogen storage and blood sugar in B₁ avitaminosis. Further indications of this are found in clinical experience. A hyperglycemia and glycosuria in depancreatized dogs which does not respond to insulin but is cured by thiamin plus riboflavin has been reported. The whole matter of vitamin B₁ deficiency in relation to sugar disturbances requires further study, as the evidence of some association of the two is strong but still obscure." Monauni² claimed that thiamine is a two-sided regulator of blood sugar, raising the level when it is subnormal and lowering it when it is elevated. Several authors³ have shown that thiamine lowers the level of blood sugar and improves the sugar tolerance curve. Unfortunately, these experiments, which are mainly the ones on which claims for a beneficial action of vitamin B₁ in diabetic patients are based, all have one failing that prevents their transfer to clinical medicine. The vitamin was given intravenously, and the blood sugar levels were determined for a period of only two or three hours.

It might seem that if the experimental administration of thiamine intravenously lowers the level of blood sugar the vitamin is indicated for diabetic patients. This is not necessarily the case, since experiments of this type should not be made the basis of clinical therapeutic measures unless it can be shown that the medication, given

From the Diabetes Clinic of the Medical Division of the Lenox Hill Hospital

1 Williams, R. R., and Spies, T. D. Vitamin B₁ and Its Use in Medicine, New York, The Macmillan Company, 1938

2 Monauni, J. Vitamin B₁ and Carbohydrate Metabolism, *Ztschr f klin Med* **132**:812, 1937

3 Gottlebe, P. Vitamin B₁ and Carbohydrate Metabolism, *Ztschr f klin Med* **133** 739, 1938. Schroeder, H. Relation of the Principal Vitamins to Carbohydrate Metabolism, *Ztschr f d ges exper Med* **101** 373, 1937. Magyar, I. Investigation of the Action of Vitamin B₁ on Carbohydrate Metabolism, *ibid* **104** 495, 1938. Barone, V. G. On the Importance of Vitamin B on Carbohydrate Metabolism, *Clin med ital* **66** 326, 1935. Wilson, A. Vitamin B₁ and Carbohydrate Metabolism, *Ztschr f klin Med* **136** 77, 1939

regularly for a long period, will improve the status of diabetic persons. To quote again from Williams and Spies: "Before any final word can be written as to the relationship which exists between vitamin B₁ and any disease affecting carbohydrate metabolism in human beings, controlled observations on a large series of cases will be necessary."

Some clinical observations have been made in which thiamine was given to diabetic patients. Mosonyi and Aszodi⁴ claimed that by prolonged administration of vitamins B₁ and C the carbohydrate tolerance of diabetic patients could be improved, as evidenced by a reduction in the dosage of insulin necessary. Unfortunately, in this study the two vitamins were given together and in varied amounts, and they were administered partly by mouth and partly intravenously. There was apparently no initial control period for comparison with the results of therapy in the 5 patients studied. In view of all these variables, the conclusions are not convincing. Von Drigalski⁵ summarized his clinical experience with 10 patients as follows: "Vitamin B₁ has no influence on glycosuria, acidosis, level of blood sugar, insulin requirement, body weight, and course of diabetes mellitus. The results of experiments on animals with B-avitaminosis cannot be applied to human diabetes." The vitamin was given for periods of only three to twenty-four days, with an average of eleven days. Unfortunately, the diet and the dosage of insulin were both changed during the experimental period, and the patients do not appear to have been well standardized prior to initiation of the experiment.

Benefit from the administration of vitamin B₁ to diabetic persons was reported in 1935 by Vorhaus, Williams and Waterman.⁶ A perusal of the protocols of the patients in whom improvement was said to have been noted shows that the diets were changed during the experimental period, that in many of the patients weight was reduced to a more desirable level, and that the hyperglycemia was actually not altered appreciably. Some of the patients were apparently deficient in vitamin B₁ at the beginning of the experiment. Most of those who were not deficient were not aided by the therapy. Two years later Vorhaus⁷

4 Mosonyi, J., and Aszodi, Z. Influencing the Islands of Langerhans Through the Vagus by Means of Vitamins B₁ and C, *Klin Wchnschr* **17** 337, 1938.

5 von Drigalski, V. W. Vitamin B as a Substitute for Insulin, *Arch f Verdauungskr* **57** 1, 1935.

6 Vorhaus, M. G., Williams, R. R., and Waterman, R. E. Studies on Crystalline Vitamin B. Observations in Diabetes, *Am J Digest Dis & Nutrition* **2** 541, 1935.

7 Vorhaus, M. G. The Present Evaluation of Vitamin B₁ Therapy, *Am J Digest Dis & Nutrition* **3** 915, 1937.

corrected the impression given in the preceding paper and gave an excellent summary of his work on this subject. He stated

In the majority of cases of true diabetes mellitus, we have seen no beneficial effect from the administration of vitamin B₁. We have actually seen an increase in blood sugar and urinary sugar output in some of these patients. However, a few of our cases showed a startling modification of the carbohydrate disturbance with lowered blood sugars and lowered urinary output. In those patients with disturbances of the carbohydrate metabolism in whom other stigmata of deficiency co-exist, such as unexplained obesity, loss of appetite, polyneuritic manifestations and diminished metabolic rates, we have obtained our best results. Until these false diabetics can be recognized easily, the use of vitamin B₁ in so-called clinical diabetes is justified only on an experimental basis.

EXPERIMENTAL METHOD

In order to determine the effect of thiamine administered orally for several weeks on the blood sugar levels of diabetic persons, an attempt was made to control the clinical experiment more carefully than had been done in the past. The following procedure was adopted: (a) The diets prescribed and the dosage of insulin were maintained without change during the entire course of the investigation, (b) a lengthy control period was instituted before administration of thiamine was started, and (c) determinations of blood sugar were made twice a day every two weeks on several occasions before, during and in most instances after the administration of the vitamin. Most of the patients changed little in weight, a fact which eliminates another source of variation in sugar tolerance. The only important factor that was changed during the entire period of experimentation, which in most cases was from fourteen to twenty weeks, was the therapeutic agent being tested.

Our routine diet of 70 Gm. of protein, 85 Gm. of fat and 150 Gm. of carbohydrate (1,645 calories)—which is approximately what most of the patients were taking—has been calculated from Cowgill's tables⁸ to contain between 307 and 335 U. S. P. (international) units of vitamin B₁. Thus most if not all of the patients in the experimental group were probably not deficient in this vitamin, since according to the usually accepted minimum the daily requirement is about 300 to 350 units for adults, provided proper gastrointestinal absorption takes place. Moreover, none of the patients had any clinical evidence of thiamine deficiency. All patients were given an additional 1,000 units of vitamin B₁ per day in the form of two 0.5 mg. tablets three times a day. This was continued without interruption for several weeks, during which time the blood sugar levels were determined at regular intervals. The

⁸ Cowgill, G. R. *The Vitamin B Requirement of Man*, New Haven, Conn., Yale University Press, 1934.

Values for Blood Sugar in Milligrams Per Hundred Cubic Centimeters

	Before Adminis- tration of Thiamine				During Adminis- tration of Thiamine				After Adminis- tration of Thiamine			
	A	M	P	M	A	M	P	M	A	M	P	M
Case 1	179		310		256		364		183		392	
Patient's age 52	134		278		185		364		157		285	
Patient's sex F	129		339		196		328		202		333	
Diet P 80 Gm , F 50 Gm , C 140 Gm												
Insulin P Z 60 units												
Weight at start 136 pounds (61.7 Kg)												
Weight at end 141 pounds (64 Kg)	144		309		212		352		181		337	Average
Case 2	88		192		96		184		83		139	
Patient's age 40	108		160		73		244		78		215	
Patient's sex F	68		174		69		125					
Diet P 70 Gm , F 85 Gm , C 150 Gm	121		235		128		190					
Insulin P Z 65 units	88		168									
Weight at start 132 pounds (59.9 Kg)												
Weight at end 132 pounds (59.9 Kg)	95		186		91		186		80		177	Average
Case 3	118		141		104		133					
Patient's age 50	85		127		89		167					
Patient's sex F	100		140		87		97					
Diet P 70 Gm , F 85 Gm , C 150 Gm	143		163									
Insulin P Z 35 units	89		121									
Weight at start 144½ pounds (65 Kg)												
Weight at end 146 pounds (66.2 Kg)	107		138		93		132					Average
Case 4	73		196		76		198		91		222	
Patient's age 69	84		70		133		183					
Patient's sex M	58		137		227		333					
Diet P 80 Gm , F 95 Gm , C 135 Gm	133		260									
Insulin P Z 65 units	112		259									
Weight at start 133 pounds (60 Kg)												
Weight at end 136½ pounds (62 Kg)	92		184		145		238		91		222	Average
Case 5	143		196		149		183					
Patient's age 68	118		142		134		206					
Patient's sex F	107		218									
Diet P 70 Gm , F 85 Gm , C 150 Gm	74		164									
Insulin P Z 25 units	132		177									
Weight at start 133 pounds (62.6 Kg)												
Weight at end 136 pounds (61.7 Kg)	115		179		142		195					Average
Case 6	136		174		143		171		131		174	
Patient's age 53	132		159		147		168		107		114	
Patient's sex M	145		200		143		144					
Diet P 70 Gm , F 85 Gm , C 150 Gm												
Insulin P Z 15 units												
Weight at start 139 pounds (63 Kg)												
Weight at end 137 pounds (62.1 Kg)	138		178		144		161		119		144	Average
Case 7	136		134		154		174		117		154	
Patient's age 56	132		168		143		168					
Patient's sex F	150		140		150		160					
Diet P 70 Gm , F 40 Gm , C 175 Gm												
Insulin P Z 15 units												
Weight at start 160 pounds (72.6 Kg)												
Weight at end 160 pounds (72.6 Kg)	139		147		149		167		117		154	Average
Case 8	113		87		97		79		111		66	
Patient's age 52	100		96		112		74					
Patient's sex F	112		82		97		78					
Diet P 40 Gm , F 40 Gm , C 120 Gm	107		79		112		79					
Insulin P Z 20 units	106		84									
Weight at start 236 pounds (107 Kg)												
Weight at end 250 pounds (113 Kg)	108		86		105		78		111		66	Average

	Before Adminis- tration of Thiamine				During Adminis- tration of Thiamine				After Adminis- tration of Thiamine			
	A	M	P	M	A	M	P	M	A	M	P	M
Case 9	196		163		140		148		132		119	
Patient's age 53	158		238		140		127		133		143	
Patient's sex F	108		134		118		133					
Diet P 85 Gm , F 80 Gm , C 150 Gm	121		174									
Insuln P Z 20 units												
Weight at start 152 pounds (68.9 Kg)												
Weight at end 155 pounds (70.3 Kg)	146		178		133		136		132		131	Average
Case 10	94		106		95		133		99		101	
Patient's age 54	94		109		91		129					
Patient's sex F	93		126		87		87					
Diet P 70 Gm , F 85 Gm , C 180 Gm					112		112					
Insuln P Z 8 units												
Weight at start 111 pounds (50.3 Kg)												
Weight at end 112 pounds (50.8 Kg)	94		114		96		115		99		101	Average
Case 11	127		164		137		210					
Patient's age 38	129		170									
Patient's sex M	126		163		Therapy discontinued because of acute rheumatic poly- arthritis							
Diet P 70 Gm , F 85 Gm , C 150 Gm	133		163									
Insuln P Z 20 units												
Weight at start 171 pounds (77.6 Kg)												
Weight at end 169 pounds (76.7 Kg)	129		165									Average
Case 12	328		476		Diabetic coma 10 days after start of administration of thiamine							
Patient's age 18												
Patient's sex M												
Diet P 100 Gm , F 100 Gm , C 200 Gm												
Insuln P Z 80, regular 15, units												
Weight at start 124 pounds (56.2 Kg)												
Weight at end ?												

In this table the following abbreviations are used P, protein, F, fat, C, carbohydrate, P Z, protamine zinc insulin

Benedict copper method⁹ was used for all determinations of blood sugar (normal value, 65 to 100 mg per hundred cubic centimeters) Blood was taken at 9 a m, before breakfast but after the injection of protamine insulin, and again at 2 30 p m, after lunch These hours were chosen because it has been repeatedly observed that in patients taking protamine zinc insulin, as were all the patients in this series, the morning level of blood sugar, observed in the fasting condition, is usually at the lowest level of the twenty-four hours, while the highest value usually occurs between 2 and 3 p m Thus with these two figures it is felt that a good concept of the twenty-four hour variation in the level of blood sugar is obtained

OBSERVATIONS

Twelve patients were started on the experimental course previously outlined, and all the important data are summarized in the table Two patients (cases 1 and 4) showed a marked elevation, and 2 (cases 5

⁹ Benedict, S R The Analysis of Whole Blood II The Determination of Sugar and of Saccharoids (Non-Fermentable Copper-Reducing Substances), J Biol Chem **92** 141, 1931

and 7) a moderate elevation, of the average level of blood sugar while taking vitamin B₁. In 3 of these 4 patients the level declined after thiamine therapy was discontinued, in the fourth case no determinations were made. In 4 patients (cases 2, 6, 8 and 10) the average level of blood sugar remained approximately the same during the period of ingestion of the vitamin as before. However, in 2 of these (cases 2 and 6) the levels became slightly lower after the medication was discontinued. One patient (case 3) showed a slightly lower level while taking thiamine, but no determinations were made after stopping its use. One patient (case 9) showed a moderate fall in the average level of blood sugar during the treatment, but the level remained just as low after cessation of treatment. In 1 patient (case 11) acute rheumatic polyarthritides developed shortly after administration of thiamine was started, and he should not, therefore, be included in a discussion of results. Another patient (case 12) was admitted to the hospital in diabetic coma ten days after commencing thiamine therapy. He was a youth of 18 with persistently high levels of blood sugar, he had always been difficult to regulate and had been in coma previously. Whether or not the administration of the vitamin had anything to do with the onset of coma on this occasion cannot be determined, and this case is therefore excluded from the series.

COMMENT

The patients in whom the effect of the experimental therapy was studied had been under observation in the diabetes clinic for at least three months before starting to take thiamine. They were probably faithful to the prescribed diet, and at any rate they probably did not change their dietary habits during the experimental period. With 2 exceptions (cases 1 and 8) the weight of all patients remained very constant throughout. During the entire period of investigation, the insulin dosage and the prescribed diet were not changed, and no infection or other factors likely to upset the carbohydrate metabolism were observed in any of the 10 completely studied cases.

The average blood sugar levels of 2 patients (cases 3 and 9) became lower while they were taking 1,000 units of thiamine daily in addition to the amount in their food. In 4 patients (cases 2, 6, 8 and 10) no significant difference was noted. Four patients (cases 1, 4, 5 and 7) showed moderate to marked elevation of the average blood sugar level while taking the vitamin. There was no apparent relation between the severity of the diabetes, as judged by the amount of insulin needed, and the change in the blood sugar level during administration of thiamine.

A statistical analysis¹⁰ of the variations in the average values for blood sugar in this series of 10 patients shows that the changes are not

¹⁰ Snedecor, G. W. Statistical Methods, Ames, Iowa, Collegiate Press, 1937.

statistically significant¹¹ Therefore the variations noted may be due entirely to chance Thus it is not permissible to claim either benefit or harm in the diabetic status of these patients as a result of administration of thiamine

There does not appear to be any doubt that patients who are deficient in vitamin B₁ and who show a concomitant hyperglycemia—"false diabetes"—will benefit from administration of thiamine¹² Diabetic patients with polyneuritis or other evidence of vitamin B₁ deficiency should receive adequate doses of the vitamin In our series there were apparently no cases of false diabetes, i e, "patients with disturbances of the carbohydrate metabolism in whom other stigmata of deficiency co-exist" It was in this type of case that Vorhaus⁷ obtained his best results

In spite of some laboratory experiments³ which seem to show that thiamine improves carbohydrate tolerance, its administration as a routine measure in the treatment of diabetes does not appear indicated¹³ Some of the patients in Vorhaus' series and in ours showed a marked increase in the average levels of blood sugar while taking vitamin B₁ In spite of the fact that the statistical analysis of the cases in this paper indicates that the rise is probably due to chance variations, one cannot escape the feeling that perhaps thiamine taken in large quantities over a long period does affect certain diabetic patients adversely As is well known at present, this medication is likely to increase appetite, strength and a general feeling of well-being, and this combination was, in fact, noted by a few of our patients Thus a diabetic patient may feel better while taking thiamine, yet because of the increased appetite, the hyperglycemia may increase unless the dose of insulin is increased Definite conclusions concerning the influence of thiamine on diabetic patients are not warranted from the small number of cases in this report, but there is no evidence of improvement in the average levels of blood sugar Additional data are desirable before attempts to state the exact role of vitamin B₁ in diabetes

11 The statistical analysis is as follows

For levels of blood sugar observed in the morning mean percentage change, +11.30, standard error of mean, 7.58, "t" (mean/standard error), 1.490

For levels of blood sugar observed in the afternoon mean percentage change, +1.90, standard error of mean, 4.76, "t" (mean/standard error), 0.400

The value for "t" in both instances is too low to be statistically significant

12 Williams and Spies¹ Vorhaus⁷

13 von Drigalski⁵ Vorhaus⁷ Smith, K. A., and Mason, H. L. Thiamin and Diabetes Mellitus, Proc. Staff Meet., Mayo Clin. **15**:529, 1940 Owens, L. B., Rockwern, S. S., and Brown, E. G. Evaluation of Vitamin B Therapy for Diabetes, Arch. Int. Med. **66**:679, 1940 Kaufman (this paper)

SUMMARY AND CONCLUSIONS

Thiamine in daily dosage of 1,000 U S P (international) units in addition to the amount in the food was given orally for periods of five to eight weeks to 10 well controlled diabetic patients

Four patients showed an elevation of the average level of blood sugar while taking thiamine, 4 showed no appreciable change, and 2 showed a lowering

Statistical analysis indicates that these variations are due to chance and not to any specific factor, such as as the therapeutic agent under investigation

Since no improvement in the average level of hyperglycemia was noted during the administration of thiamine, it is concluded that use of this vitamin is not indicated as a routine measure for diabetic patients

Dr F B Peck, of Eli Lilly & Co, and Drs J D Ralston and A D Emmett, of Parke, Davis & Co, aided in the preparation of this manuscript

Parke, Davis & Co supplied all the vitamin B₁ (crysto-vibex, 0.5 mg tablets) used in these experiments

RELATION OF FATTY ACIDS AND BILE SALTS TO THE FORMATION OF GALLSTONES

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In a previous report¹ some of the chemical differences between the bile of certain domestic animals and that of human beings were discussed. By fractionating the bile of the dog and sheep, animals in which gallstones are not formed ordinarily, it was observed that the cholesterol solvent capacity of the bile could be isolated in the saponifiable or fatty acid fraction. Quantitative analysis of bile from the gallbladders of these animals showed that the saponifiable fraction was relatively high in the dog and sheep but low in the ox and hog. Similar analysis of human bile showed that the concentration of the saponifiable fraction was extremely low in proportion to the nonsaponifiable or cholesterol fraction. These findings, along with the previous work of Walsh and Ivy,² suggested that the fatty acids in the bile play an extremely significant role in maintaining cholesterol in solution and in preventing the formation of gallstones. The studies further indicated that the action of fatty acids in this connection is much greater than the action of the bile salts or bile acids.

The foregoing observations were based on one thousand, eight hundred and forty comparative experiments which were performed with standardized gallstone tablets prepared from the material obtained by pulverizing four thousand human gallstones of mixed variety

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1 Dolkart, R. E., Jones, K. K., and Brown, C. F. G. Chemical Factors Concerned in the Formation of Gallstones, *Arch. Int. Med.* **62**:618 (Oct.) 1938

2 (a) Walsh, E. L., and Ivy, A. C. Observations on the Etiology of Gallstones, *Ann. Int. Med.* **4** 134, 1930. (b) Walsh, E. L. Etiology of Gallstones, *Arch. Path.* **15** 698 (May) 1933

Analysis of the tablets showed them to contain 70.6 per cent cholesterol. In determining the cholesterol solvent capacity of a given solution, twenty tablets were shaken separately in each of the solutions to be tested, the average loss of weight was determined and the standard error computed. Although the data clearly indicated the greater activity of the fatty acids over the bile salts as cholesterol solvents, several interesting questions arose which merited further investigation. For example, it would be theoretically possible for the various solutions which were used in these experiments to dissolve out some of the noncholesterol components of the stones, permitting the disintegration rather than the true solution of these stones artificially prepared from the powdered gallstones. The varying effects of changes in surface tension brought about by the different substances employed was another question which arose. Therefore, in order to check these possibilities and to show definitely that it is the solubility of cholesterol from the stones that brings about the dissolution of the gallstone in these solvents, it seemed advisable to repeat the experiments previously made on synthetic gallstones on the stones formed in the same way from pure cholesterol.

METHOD

Because of the possibility of error due to the dissolution of noncholesterol components, the tablets employed in these experiments were prepared from pure cholesterol. With a small amount of talc as a binder, the cholesterol was compressed in a pharmaceutical tablet press into uniform tablets weighing from 180 to 200 mg. Each tablet was wrapped in a small gauze bag and suspended in the solution to be tested in a small Erlenmeyer flask. The flasks were mounted in a mechanical shaking device rotating at 25 to 30 half revolutions per minute and placed in an incubator maintained at a constant temperature of 70 C, in order to hold the fatty acids tested in solution. All solutions were buffered to a p_H of 10. Each experiment consisted of determining the weight loss of ten tablets shaken separately in aliquot parts of the solution to be tested. The average weight loss occurring in each solution after shaking for seven days was determined, and the standard error was computed.

RESULTS

Table 1 shows the comparative rate of dissolution of the artificial gallstone and the synthetic cholesterol stone in the sodium soaps of oleic, palmitic, stearic, myristic, lauric and linoleic acids, the fatty acids occurring most commonly in bile. It is evident from these data that the cholesterol stone is dissolved in these solutions as well as, if not better than, the stone made from the powdered gallstones.

Table 2 shows that the various bile salts which constitute the usual bile salt content of the bile have much the same solvent action on the cholesterol stones as they do on the synthetic gallstones, but to a some-

what lesser degree. The difference is so slight, however, that it may be within the limits of experimental error.

A comparison of table 1 with table 2 discloses the fact that the fatty acids are better solvents for cholesterol than are the bile salts.

The results in table 3 reveal two fundamental points. In the first place, the action of the bile salts as a cholesterol solvent is unrelated to

TABLE 1—*Comparison of Rates of Solution of Artificial Gallstones and Cholesterol Stones in Solutions of Fatty Acids as Soaps*

Solution	Rate of Solution (in per Cent) of Standard Gallstones		Rate of Solution (in per Cent) of Cholesterol Stones	
	1 per Cent Solution	5 per Cent Solution	1 per Cent Solution	5 per Cent Solution
Sodium laurate	—52.1	—67.9	—51.0	—100.0
Sodium myristate	—48.6	—71.0	—81.4	—100.0
Sodium stearate	—32.4	—48.6	—14.4	—28.5
Sodium palmitate	—13.1	—53.4	—15.7	—27.1
Sodium oleate	—33.8	—64.6	—28.8	—59.3
Sodium linoleate	—11.2	—16.6	—14.6	—64.4

Standard errors were computed but in all cases were of such small magnitude, varying from 0.28 to 1.31 per cent for the standard gallstones and from 0 to 3.72 per cent for the cholesterol stones, that the limiting values were all significant. For the standard stones each figure represents the average of twenty separate experiments. For the cholesterol stones each figure represents the average of ten separate experiments.

TABLE 2—*Comparison of Rates of Solution of Artificial Gallstones and Cholesterol Stones in Solutions of Bile Salts*

Solution	Rate of Solution (in per Cent) of Standard Gallstones		Rate of Solution (in per Cent) of Cholesterol Stones	
	1 per Cent Solution	5 per Cent Solution	1 per Cent Solution	5 per Cent Solution
Sodium carbonate—control		—0.66		—0.12
Sodium cholate	—5.1	—19.9	—0.8	—23.0
Sodium taurocholate	—3.9	—12.2	—0.5	—6.1
Sodium glycocholate	—3.0	—9.6	—1.3	—3.4
Sodium desoxycholate	—2.8	—19.1	—4.2	—27.0
Sodium dehydrocholate	—0.3	—1.5	—0.3	—0.3
Sodium dehydrodesoxycholate	—2.2	—3.7	—0.2	—0.2
Mixed sodium ketocholates (ketochole)	—5.8	—10.3	—3.3	—8.3

the surface tension of their solutions. In the second place, and more important, it may be observed that in each case the weight loss can be almost wholly accounted for by the amount of cholesterol recovered from the solutions in which the stones were shaken, indicating that mechanical disintegration was not responsible for the weight loss.

A comparison of the rates of dissolution obtained in the alkaline solutions of the fatty acid soaps alone and the bile salts alone, as shown

in figure 1, with the rate of dissolution in combination of bile salts and fatty acids, as shown in figure 2, shows the following facts

1 Lauric and myristic acid soaps, with their low molecular weight, have several times the solvent action of the unsaturated oleic and linoleic acid soaps, with a higher molecular weight, and these in turn are markedly superior to the soaps of the saturated fatty acids, palmitic and stearic

2 The unconjugated bile acids, desoxycholic and cholic acids, are superior to the conjugated taurocholic and glycocholic acids in their solvent capacity for cholesterol

TABLE 3—*Rates of Solution of Standardized Cholesterol Stones in the Various Solutions of Bile Salts*

Solution	Surface Tension, Dynes per Centimeter	Actual per Cent of Weight Loss	Per Cent of Weight Lost Calculated as Cholesterol	Per Cent of Cholesterol Recovered from Solutions
5% Sodium carbonate control	39.0	0.12	0.09	None
1% Sodium cholate	46.7	0.77	0.64	Trace
1% Sodium glycocholate	43.9	1.29	1.07	1.09
1% Sodium taurocholate	43.2	0.51	0.43	0.43
1% Sodium desoxycholate	45.2	4.21	3.76	3.92
1% Sodium dehydrocholate	46.2	0.25	0.23	Trace
1% Sodium dehydrodesoxycholate	47.0	0.18	0.15	Trace
1% Mixed sodium ketocholanates (ketocho)	46.5	3.30	2.74	2.57
5% Sodium cholate	46.3	23.00	20.0	12.24
5% Sodium glycocholate	41.3	3.38	2.80	2.83
5% Sodium taurocholate	40.2	6.13	5.35	4.25
5% Sodium desoxycholate	44.3	27.10	24.10	18.60
5% Sodium dehydrocholate	46.0	0.33	0.27	Trace
5% Sodium dehydrodesoxycholate	46.5	0.23	0.19	Trace
5% Mixed sodium ketocholanates (ketocho)	46.0	8.33	6.91	8.22

Standard errors were computed as in table 1. Each figure represents an average of ten separate experiments.

3 An increase in the bile salt concentration from 1 to 5 per cent, while maintaining the fatty acid at the 1 per cent level, brings about an increase in the amount of dissolved cholesterol in the presence of desoxycholic acid and cholic acid but does not bring about a corresponding increase in the presence of taurocholic or glycocholic acids.

4 An increase in fatty acid concentration from 1 to 5 per cent, with the bile salt at the 1 per cent level, causes a marked increase in the solvent activity of the bile salt—fatty acid soap mixture in all the mixtures studied.

5 An increase of bile salt in the mixture from 1 to 5 per cent, with the fatty acid at the 5 per cent level, shows some conflicting results. In the mixtures with the unconjugated desoxycholic acid, lauric, myristic and palmitic acids show an increase in solvent action and stearic and

linoleic acids a decrease, while oleic acid shows little change Cholic acid produces no effect on solubility with lauric and myristic acids but a decrease in solubility with all the others The addition of taurocholic

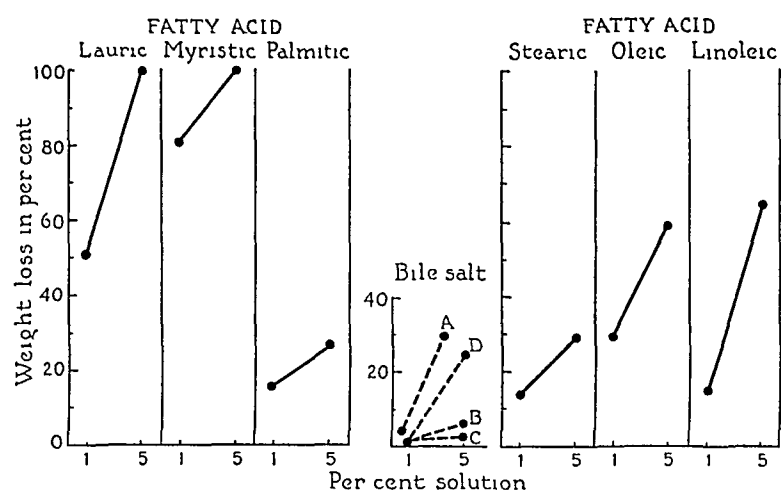


Fig 1—Per cent of weight loss of cholesterol tablets in 1 and 5 per cent solutions of bile salts and fatty acids A, sodium desoxycholate B, sodium taurocholate C, sodium glycocholate D, sodium cholate

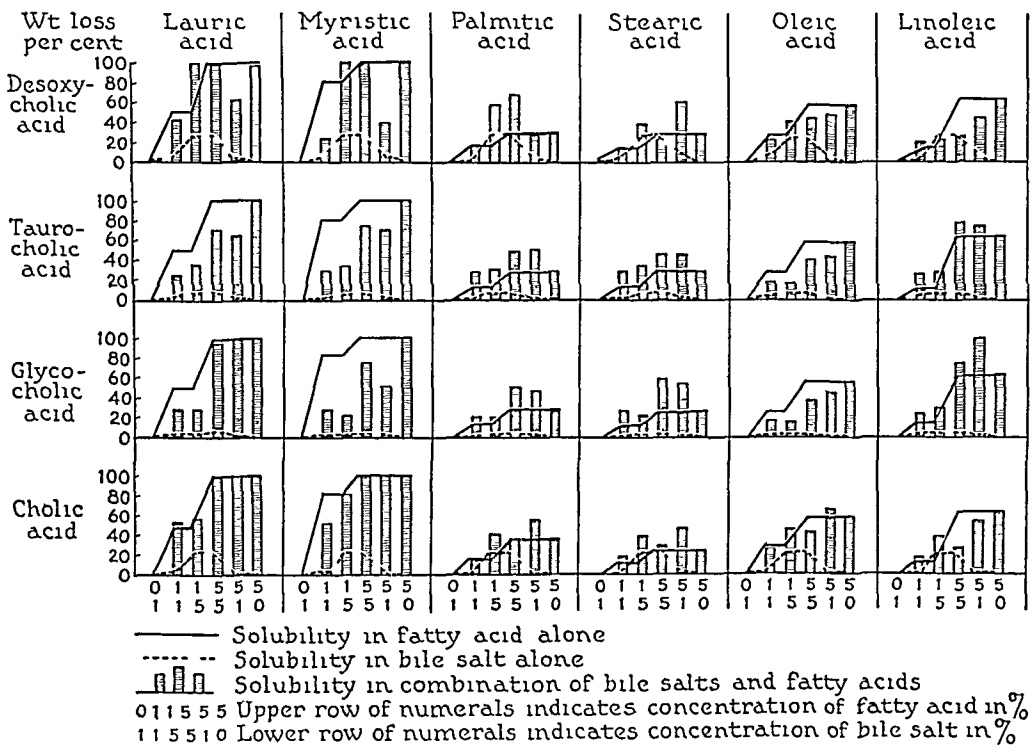


Fig 2—Per cent of weight loss of cholesterol tablets in solutions of bile salts and of fatty acids and in solutions of bile salts and fatty acids combined

acid produces little effect on the solubility of cholesterol in any of the fatty acids Glycocholic acid effects no change in solubility when added to lauric, palmitic, stearic and oleic acids, whereas with myristic

the mixture shows a definitely increased solvent action, and with linoleic acid, a decreased solvent action of equal magnitude

6 Tables 2 and 3 show that the oxidation of the unconjugated bile acids to dehydrocholic and dehydrodesoxycholic acid reduces the solvent ability which the unoxidized bile acids possessed. The mixed keto-cholanic acids in the form of ketochol³ show approximately a third of the solvent action of cholic acid. At present there is no explanation for the increased solubility effect of ketochol over that of the individual oxidized bile acids.

COMMENT

It is generally conceded that the essential stone-forming substance in biliary calculi is the crystalline cholesterol that binds pigment, protein, calcium salts and tissue debris into a solid concretion. Without this interlacing framework of cholesterol crystals these substances form merely a "colloidal mush" in the gallbladder, which readily flows through the cystic duct on pressure. The formation of stones, therefore, depends on the presence of crystalline cholesterol, and this in turn depends on the amount of cholesterol in the bile and the readiness with which crystallization can occur.

According to the conclusions of Greene and Hotz,⁴ who recently summarized the literature, an increased amount of cholesterol in the bile is due either to an increased cholesterol metabolism in the body or to some change in the function of the liver. The solvent capacity of bile for cholesterol is variously ascribed to the physicochemical property of bile, which can lower surface tension and make possible colloidal solutions, the combining power of bile salts for cholesterol and the content of soaps and fatty acids. Lichtwitz,⁵ the chief proponent of the first conception, pointed to the relation of p_H and protein content of bile and the amount of colloidal material suspended in the bile but could not adequately explain the solution of cholesterol by this mechanism.

Wieland and Sorge⁶ suggested that the choleic acid principle discovered by them in 1916 might explain the solvent action of bile for cholesterol. It has been shown, however, that this combination of fatty acid and desoxycholic acid has no marked solvent action on cholesterol. Other compounds of this kind have not been isolated, according to

3 Supplied to us by G. D. Searle & Co., Chicago.

4 Greene, C. H., and Hotz, R. The Liver and Biliary Tract. A Review for 1938, *Arch. Int. Med.* **63**: 778 (April) 1939.

5 Lichtwitz, L. Prinzipien der Konkrementbildung, in Bethe, A., von Bergmann, G., Embden, G., and Ellinger, A. *Handbuch der normalen und pathologischen Physiologie*, Berlin, Julius Springer, 1929, vol. 4, p. 591.

6 Wieland, H., and Sorge, H. Untersuchungen über die Gallensäuren, *Ztschr. f. physiol. Chem.* **97**: 1, 1916.

Fieser⁷ However, loose compounds similar to choleic acid may be formed in bile with glycocholic and taurocholic acids Verzar and McDougall⁸ claimed that such combinations are formed and that this formation is the mechanism whereby fat and cholesterol are carried through the intestinal wall and transported in the portal circulation

Cholesterol is readily soluble in fats of all kinds and exceedingly soluble in fatty acids Fats and fatty acids as such are insoluble in water Fats can be emulsified into colloidal solutions, and fatty acids can be combined with alkali to form soluble soaps or can be built into phospholipids that are soluble in water to a certain extent These have been shown by Spanner and Bauman⁹ to be much more soluble in bile salt solutions

Walsh and Ivy^{2a} have shown that the saponifiable fat in bile is the important factor in dissolving and holding cholesterol in solution Reinhold, Ferguson and Hunsberger¹⁰ have observed that at least half the total solids in bile are bile salts and that the remainder is lipoidal They concluded from their studies that a lowered bile salt concentration in the bile leads to a decreased solvent action for fatty acids and cholesterol Our data indicate strongly that the fatty acids and the lipids of the bile are chiefly concerned in determining the solubility of cholesterol in bile

The mechanism by which free fatty acids are held in solution in an alkaline hepatic bile as soap is easy to understand It is not so easy to explain the solubility of these fatty acids in an acid gallbladder bile at a p_H at which fatty acids are normally precipitated The exact nature of the lipid in bile is not certain Most probably there is a combination of fatty acids, bile salts and phospholipids Lecithin and neutral fat do not seem to be present¹¹ The lipoidal content of bile is held in such form that it cannot be readily extracted by fat solvents until the bile has been decomposed by treatment with acid or alkali From this we can only conclude at this time that the solution of fat in bile is brought about in some unknown manner by means of the bile salts in the bile

The data shown in figure 2 indicate that a bile salt-fatty acid complex is formed and that disturbances in either portion of the complex may

7 Fieser, L F The Chemistry of the Natural Products Related to Phenanthrene, New York, Reinhold Publishing Corporation, 1936, p 131

8 Verzar, F, and McDougall, E J Absorption from the Intestine, New York, Longmans, Green & Co, 1936, p 163

9 Spanner, G O, and Bauman, L The Behavior of Cholesterol and Other Bile Constituents in Solutions of Bile Salts, *J Biol Chem* **98** 181, 1932

10 Reinhold, J G, Ferguson, L K, and Hunsberger, A The Composition of Human Gallbladder Bile and Its Relation to Cholelithiasis, *J Clin Investigation* **16** 379, 1937

11 Jones, K K, and Sherberg, R O Are Neutral Fat and Lecithin Present in Gallbladder Bile? *Proc Soc Exper Biol & Med* **35** 535-537, 1937

result in changes in cholesterol solubility. Owing to the slight solvent activity of the bile salt complex, alteration of the concentration of this component has only minor effects, while even slight changes in fatty acid content make a significant difference in solvent capacity one way or the other.

Studies¹² made on pathologic human bile have shown that fluctuations in the fatty acid fraction occur concomitantly with the fluctuations in the bile salt fraction. The amounts of both bile salts and fatty acids eliminated in the bile are decreased during hepatic injury and tend to increase in the bile as the condition of the liver improves. Further progress in determining the cause of gallstones seems to be definitely related to obtaining a more complete knowledge of the role of the fatty material in bile and the fate of the fat when cholesterol stones are formed.

SUMMARY AND CONCLUSIONS

1 The data from these experiments confirm previous work in showing that the fatty acids are the important factor in bile for holding the cholesterol in solution.

2 The conjugated bile salts by themselves exert only a small effect on the solubility of cholesterol. The unconjugated nonoxidized bile salts have a greater solvent activity than the conjugated, but it is still far below that of the fatty acids. This activity is lost when the unconjugated bile acids are oxidized.

3 The smaller molecular or short chain lauric and myristic acids have more solvent ability than the longer chain palmitic and stearic acids. The unsaturated linoleic and oleic acids have more solvent action than the saturated stearic acid with the same length carbon chain.

4 The bile salts have a variable effect on the solubility of cholesterol when mixed with the fatty acid. In most instances the addition of bile salts increased the solubility, in other instances the addition of the bile salts decreased the efficiency of the fatty acids as cholesterol solvents. The explanation for this cannot be had from these experiments. There is a suggestion that the bile salts and the cholesterol may compete for solution in the fatty acid, especially in the presence of the unconjugated acids.

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¹² Dolkart, R. E., Lorenz, M., Jones, K. K., and Brown, C. F. G. Unpublished data.

SYNDROME OF SUBNORMAL CIRCULATION IN AMBULATORY PATIENTS

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AND

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PHILADELPHIA

In this communication we describe the signs and symptoms commonly found in ambulatory hospital patients who have subnormal basal or resting circulations, ascertained by estimating their cardiac output. The clinical syndrome exhibited by such patients is definite enough to permit the diagnosis of this abnormality in many instances when methods of estimating cardiac output are not available.

Determinations of cardiac output were begun in this hospital in 1927 by means of the ethyl iodide method¹. At first extremely slow and laborious, the speed of operation was later increased by adaptation of the katharometer to our analytic needs by Donal and Gamble². In all, 335 subjects were tested by this method over a period of eight years³.

The advent of the ballistocardiogram⁴ permitted us to estimate cardiac output with a speed and ease of operation equal to those of other routine

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1 Starr, I, Jr, Collins, L H, and Wood, F C. Studies on the Basal Work and Output of the Heart in Clinical Conditions, *J Clin Investigation* **13** 13-43 (Jan) 1933

2 Donal, J S, Jr, Gamble, C J, and Shaw, R. The Cardiac Output in Man. An Adaptation of the Katharometer for the Rapid Determination of Ethyl Iodide in Estimations of Cardiac Output by the Ethyl Iodide Method, *Am J Physiol* **109** 666-681 (Oct) 1934

3 Starr, I, Donal, J S, Jr, Margolies, A, Collins, L H, and Gamble, C J. Studies of the Heart and Circulation in Disease. Estimations of Basal Cardiac Output, Metabolism, Heart Size and Blood Pressure in Two Hundred and Thirty-Five Subjects, *J Clin Investigation* **13** 561-592 (July) 1934. Starr, I, Gamble, C J, Margolies, A, Donal, J S, Jr, Joseph, N R, and Eagle, E. A Clinical Study of the Action of Ten Commonly Used Drugs on Cardiac Output, Work, and Size. On Respiration, on Metabolic Rate, and on the Electrocardiogram, *ibid* **16** 799-823 (Sept) 1937

4 Starr, I, Rawson, A J, Schroeder, H A, and Joseph, N R. Studies on the Estimation of Cardiac Output in Man, and of Abnormalities of Cardiac Function, from the Heart's Recoil and the Blood's Impacts. The Ballistocardiogram, *Am J Physiol* **127** 1-28 (Aug) 1939

clinical methods In the last three years the total experience has increased to over 1,000 cases About 300 subjects were healthy persons, the remainder being patients in the medical division of the University Hospital

During this prolonged investigation we had in mind both immediate and remote objectives The results analyzed from the former point of view have been published from time to time⁵ We shall now consider these old results and a much larger number of new ones from another point of view Normal standards for healthy persons have been established The number of subjects having a subnormal cardiac output has now exceeded 100 We propose to analyze the data obtained from the first 100 of these cases and discuss the clinical and physiologic significance of this abnormality

In this prolonged investigation many persons other than ourselves have contributed to the results Some of their names have appeared as co-authors in earlier publications⁷ The orthodiagrams and electrocardiograms were made by members of the staff of the Robinette Foundation The former were prepared by Drs A Margolies, W A Jeffers, J Edeiken and M M Livezey Dr F C Wood assisted us in interpreting and classifying the electrocardiograms One of us (Jonas) has supervised all estimations of basal metabolic rate performed during the last three years

METHODS

When cardiac output was estimated by the ethyl iodide method the tests were performed before breakfast with the patient supine under strict conditions of basal metabolic rate With the advent of the ballistocardiogram our procedure changed to the extent that we made all tests in the morning or afternoon after a resting period of at least fifteen minutes and never within two hours of a meal The results obtained under the latter conditions were nearly identical with those secured under strictly basal conditions, so convenience dictated the latter course There was no disagreement between the results secured by the two methods, and the main conclusions of this paper are warranted by the results obtained from either Of the 100 cases included in this investigation, the condition was detected by ethyl iodide in 26 and by the ballistocardiogram in the remainder

In the early estimations, basal metabolic rates were estimated by analysis of expired air For the last three years they have been determined by the Benedict-Roth technic

The size of the heart was estimated by the orthodiagram

Normal standards for cardiac output as estimated by the ballistocardiogram⁸ and our data on normal subjects obtained by the ethyl iodide method⁵ have been

5 Starr, Collins and Wood¹ Starr and others³

6 Footnote deleted

7 Starr, Collins and Wood¹ Donal and others² Starr and others⁴

8 Starr, I, and Schroeder, H A The Ballistocardiogram II Normal Standards, Abnormalities Commonly Found in Diseases of Heart and Circulation, and Their Significance, *J Clin Investigation* 19 437-450 (May) 1940

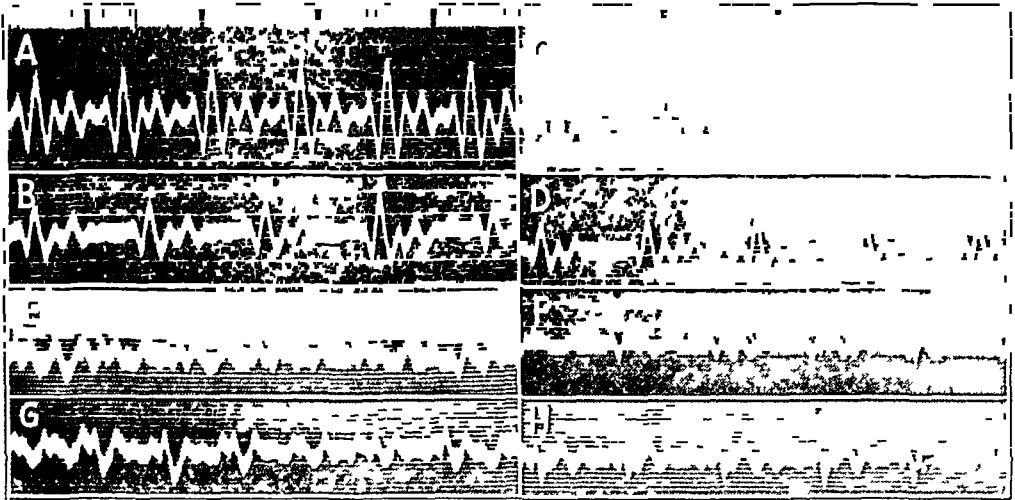


Fig 1—Ballistocardiograms of 4 normal persons compared with those of 4 patients with subnormal circulation to illustrate the differences between the groups. With reservations as regards age, body weight and pulse rate (Starr and others,⁴ Starr and Schroeder⁸) the amplitude of the records reflects the cardiac output. The average normal cardiac output is 23 cc per minute per pound of body weight, and the normal limits are ± 22 per cent.⁸ The records shown are reduced to about one-half actual size.

A, record of I S, a man aged 44. His height was 6 feet (182.8 cm), his weight, 185 pounds (83.9 Kg). The blood pressure was 120 systolic and 75 diastolic (normal). The cardiac output was $+9$ per cent. B, record of J S, a man aged 53. His height was 5 feet 7 inches (170 cm), his weight, 152 pounds (68.9 Kg). The blood pressure was 125 systolic and 80 diastolic (normal). The cardiac output was $+9$ per cent. C, record of E S, a woman aged 28. Her height was 5 feet 3 inches (160 cm), her weight, 123 pounds (55.8 Kg). The blood pressure was 115 systolic and 65 diastolic (normal). The cardiac output was identical with the normal average. D, record of K C, a woman aged 50. Her height was 5 feet 4 inches (162.5 cm), her weight, 140 pounds (63.5 Kg). The blood pressure was 148 systolic and 90 diastolic (normal). The cardiac output was -13 per cent. E, record of C M, a woman aged 50. Her height was 5 feet $\frac{1}{2}$ inch (152.6 cm), her weight, 164 pounds (74.4 Kg). The blood pressure was 190 systolic and 125 diastolic. There was syphilis, hypertension and acromegaly. The chief complaint was dizziness. The cardiac output was -52 per cent. F, record of M L, a woman aged 48. Her height was 5 feet 9 inches (175 cm), her weight, 129 pounds (58.5 Kg). The blood pressure was 115 systolic and 70 diastolic. There was neurocirculatory asthenia with rare attacks of paroxysmal tachycardia. At the time of testing the patient was in normal rhythm. The cardiac output was -39 per cent. G, record of J C, a man aged 34. His height was 5 feet 4 inches (162.5 cm), his weight, 182 pounds (82.6 Kg). The blood pressure was 260 systolic and 170 diastolic. There was malignant hypertension. The cardiac silhouette area was 98 sq cm (predicted normal 107 sq cm). The cardiac output was -43 per cent. H, record of I F, a woman aged 41. Her height was 5 feet 1 inch (154 cm), her weight, 165 pounds (74.8 Kg). The blood pressure was 155 systolic and 80 diastolic. There was neurocirculatory asthenia. The cardiac output was -52 per cent.

published These results indicate that the lower limit of cardiac output for normal persons is 18 cc per minute per pound of body weight, 22 per cent below the normal average The patients to be discussed all had cardiac outputs smaller than this, and the distribution of the results is shown in figure 2 Typical ballistocardiograms are shown in figure 1

In the preliminary report of this work,⁹ short cut methods were employed to calculate cardiac output from ballistocardiograms, and conclusions were based on much fewer data on normal standards When results secured by the more exact method⁸ were applied to the completed normal standards, 12 subjects of the original

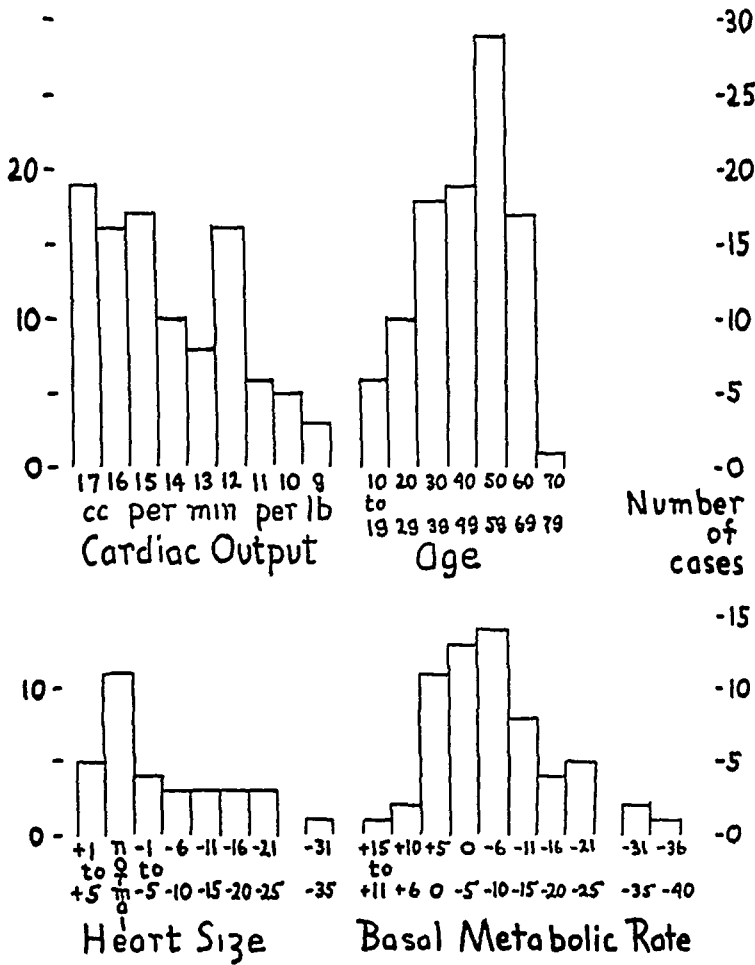


Fig 2—Frequency diagrams of patients with subnormal circulation The data on “heart size” have been limited to those obtained from patients without organic heart disease and without hypertension In the column marked normal the silhouette area was judged to be in the center of the normal range, but it was not exactly measured

series proved to have had circulation just within normal limits Their cases have been omitted from the present series and replaced by 12 in which the values were lower The small differences between the preliminary and the final results are due to this fact

9 Starr, I On the Clinical Characteristics of Patients with Subnormal Circulations in the Absence of Acute Heart Failure, Tr A Am Physicians 54 163-169, 1939

Selection of Cases—All subjects were resident patients or outpatients at the University Hospital, and the great majority came from the medical wards, having been selected by one of us (Starr) from patients under his care

Since the cardiac output becomes zero at death, it is inevitable that a patient dying from any cause will have subnormal circulation. Under these circumstances the condition would have little scientific interest. To avoid this difficulty we have included only ambulatory patients in this series.

There are a few situations with which our methods are not fitted to deal. We distrust the results secured with ethyl iodide in cases of advanced pulmonary disease. In certain cases of heart disease the ballistocardiogram gives results difficult to translate into cardiac output, and when there is regurgitation of blood the results refer to the total systolic cardiac output rather than to the amount which contributes to the circulation. When such difficulties arose the cases were omitted from this series. With these exceptions the results may be expected to provide a fair sample of the ambulatory population of the medical ward.

RESULTS

An analysis of the data obtained from this group of 100 patients with subnormal circulation follows.

Sex—Forty-two of the patients were men, and 58 were women. The disproportion of women is probably due to the facts that the terms of service of one of us (Starr, who selected the subjects) in the women's ward exceeded those in the men's and that he tended to study the cases with which he was most familiar.

Age—The age distribution of the group is shown in figure 2. The condition was most frequently found in the decade between 50 and 59, but the incidence spread throughout adult life.

Diagnoses—When there were multiple diagnoses we have classified the case under the most important heading which concerned the circulation. Thus, a case of diabetes with hypertension is classified only under the latter head, a case of angina pectoris with hypertension is classified as the former.

The largest single group consisted of 30 cases of primary cardiac disease. In the majority of these (18) the patients had either recovered from cardiac infarcts or suffered from angina pectoris. Only 5 had rheumatic heart disease, and none had syphilitic heart disease. In 5, heart block was the outstanding finding, the cause being uncertain in all of them. One patient with a calcified pericardium and 1 with congenital heart disease completed this group.

The group next in size consisted of 28 patients with hypertension, all having a systolic pressure in excess of 170 mm of mercury, a diastolic pressure over 100 mm or both.

The third group contained 19 patients in whom nothing abnormal was found by any of the routine hospital tests. In the cases of 17 of these the diagnosis of functional heart disease or that of neurocirculatory

asthenia was justified, the complaints of the remaining 2 centered about the gastrointestinal tract

Next in size was a group of 11 patients with endocrine diseases. Four had diabetes, and 4 others had undergone partial thyroidectomies for hyperthyroidism. Two were adjudged to have pituitary syndromes, though the diagnosis was far from proved. The last was a patient with Addison's disease recovering from a crisis.

The remainder of the entire group consisted of 5 elderly persons showing little but arteriosclerosis, 3 patients who were convalescent from pneumonia, typhoid fever and catarrhal jaundice respectively, single patients with migraine, malnutrition and postural hypotension and, finally, a patient having attacks suggesting atypical epilepsy but with a cardiac lesion in addition.

These patients with subnormal circulation bore the following numerical relation to patients with similar conditions whose cardiac output was normal. Of all the patients with coronary heart disease that we have studied, almost exactly half had circulation below the normal range, and in some the circulation was extremely subnormal. Of the remainder the great majority had circulation very little above the lower limit of normal. In contrast to this, only 10 per cent of the patients with rheumatic heart disease studied had subnormal circulation. This figure may be somewhat too small, as the ballistocardiogram indicates the total cardiac output, which includes the blood later regurgitated through leaking valves, but one can confidently state that subnormal circulation is encountered frequently in cases of coronary disease and much less frequently in cases of valvular heart disease.

Patients with hypertension and subnormal circulation constituted about one third of the total. Patients with "functional heart disease" included in the subnormal series were one half of those studied, but many of the remainder had circulation close to the lower limit of normal.

Symptoms—Almost all (90 per cent) of the patients with subnormal circulation regarded themselves as unduly weak and easily fatigued, in 17 cases extreme weakness was the chief complaint.

The symptom next in frequency was dyspnea on exertion, which was noted by 64 patients. Nineteen of the patients who did not report this symptom took no exercise because of either angina pectoris or peripheral vascular disease, and so they were not in a position to tell whether they had undue dyspnea on exertion. If these are omitted from the total, 79 per cent complained of this symptom.

The group's most characteristic symptom was attacks of dizziness, present in 73 per cent. Most characteristically this occurred when the patients were upright, especially when they had just assumed that position, but a few insisted that they occasionally had dizziness when

lying down as well. Close questioning of the intelligent disclosed that there was no sensation of rotation and no true vertigo. Indeed, the sensation was sometimes described as attacks of light headedness, sometimes as attacks of faintness and sometimes just as "spells." This difficulty was the major complaint in 26 of the cases.

Undoubtedly related to these attacks was the frequency of fainting in the group. Fourteen patients were subject to repeated attacks of fainting, and 5 others had fainted once or twice.

Forty of the patients considered themselves nervous, with 8 this was a major complaint. Diagnoses which had been made in certain cases were conversion hysteria, anxiety neurosis, neurasthenia and psychoneurosis.

No other symptoms seemed characteristic of the group. Many patients complained of frequent headaches of slight degree, but only 1 had severe headaches. Coldness of the extremities was a complaint in only 7 cases, undue suffering from hot or cold weather was reported by only 3 patients.

Physical Examination — Examination disclosed little significant information. Arteriosclerosis was the most common finding, being slight in 16 patients, moderate in 13 and marked in 10. Certainly many patients with arteriosclerosis would be found in any group of patients with corresponding ages.

In 26 cases the examining physician noted that the heart sounds were either distant or of poor quality. The pulse was recorded as weak in only 5 cases. When hypertension was present the pulse was always strong, quite irrespective of the size of the circulation.

In only 1 case was the resting heart rate over 100 per minute, in 4 it was between 90 and 100. If the cases of heart block are omitted, the rate was between 55 and 65 in 15 cases and between 50 and 55 in 6. Therefore, although highly abnormal pulse rates were not found except in the cases of heart block, it is evident that the tendency is toward slow rather than rapid rates in patients with subnormal circulation.

Unusually low pulse pressure, once believed to be an indication of subnormal cardiac output, did not prove to be so. The lowest pulse pressures were 28 mm. of mercury, encountered in 2 cases, and 30 mm., encountered in 4.

The venous pressure was carefully studied in each case by inspection of the veins of the neck and by raising and lowering the hand while observing the level at which the veins filled and emptied. In no case was it abnormally elevated. On the contrary, the veins often would not distend when the hand was dependent, and so we could not get a satisfactory level of emptying when it was raised. Evidently the venous pressure is either normal or low in these cases.

Special Tests—Electrocardiograms were made in 80 cases. In 28 the records were normal or showed nothing more than axis deviation or an occasional extrasystole. Minor Variations from Normal. Changes in the T wave and slight slurring of the QRS complex were found in 26 cases. Major Abnormalities. Permanent arrhythmias, bundle branch block, evidence of cardiac infarction and major abnormalities of the QRS complex were found in 26 cases. As one would expect, there was no invariable relation between the cardiac output and the electrical record. When the heart was seriously diseased abnormalities were usually shown by both methods. But in some cases the electrocardiogram was normal although the circulation was greatly reduced and in others highly abnormal with the circulation normal or above, so it has not proved of value in detecting cases of subnormal circulation.

Fluoroscopic evidence of the size of the heart was secured in 61 cases. In 17 instances the operator believed the cardiac silhouette to be entirely normal, and only this fact was recorded, in the remaining 44 cases orthodiagrams were drawn and measured. Twenty-seven patients with hypertension and subnormal circulation were examined, and 21 of them had cardiac silhouettes within the normal range. In contrast to this, the patients with hypertension and normal circulation tended to have hearts which were much enlarged, and their cases will be the subject of a subsequent report. The sizes of the hearts of the 34 patients without hypertension or organic heart disease are given in figure 2. These hearts were either within or below the normal range, and some were extremely small.

The basal metabolic rate was estimated in 62 cases, and the distribution of the results is shown in figure 2. In the great majority of these (50 cases) the results were well within the normal range, and in none were they above normal. But the group does not have a normal distribution about zero, for patients having rates between -6 and -10 per cent of the calculated normal basal metabolic rate were found with the greatest frequency, and in 12 cases the rates were below the accepted normal limit. Unquestionably the tendency is toward a low metabolic rate when the circulation is subnormal.

Of the 12 patients for whom the results were subnormal, 2 had undergone subtotal thyroidectomies for hyperthyroidism, and 1 had the clinical signs of myxedema and will be described in detail. Of the others, 5 had no other diagnosed condition than neurocirculatory asthenia, and the remainder consisted of single patients with heart block, angina pectoris, essential hypertension and postural hypotension.

COMMENT

In comparison with the quantitative procedures used by chemists and physicists, the methods for determining cardiac output are extremely crude, and, as they cannot be tested by the estimation of known quan-

tities, their accuracy cannot be stated in mathematical terms. Nevertheless, our methods seemed entirely adequate for the purpose we had in mind, i e., to divide human subjects into two groups, those with normal and those with subnormal circulation. For such a purpose they are certainly far superior to the means ordinarily used by clinicians to gain insight into the amount of the circulation.

The Syndrome—From the data given one may describe a syndrome characteristic of patients with subnormal circulation. The most distinctive symptom is attacks of dizziness or light headedness in the upright position, many have repeated attacks of fainting as well. They consider themselves to be weak, easily fatigued and unduly dyspneic on exertion, and many are very nervous. Physical examination adds little evidence to support the diagnosis, though weak or distant heart sounds in the absence of emphysema may excite suspicion. Palpation of the pulse may mislead one, the examiner detecting a change in pressure which has no necessary relation to blood flow. Arteriosclerosis is often present in patients past middle life. In this group of ambulatory patients the size of the heart tends to be either within or below normal limits, and the basal metabolic rate is likewise normal or below.

Our confidence in the propriety of considering these symptoms as characteristic of subnormal circulation was much increased by an experience with a patient who had repeated periods of heart block of hours' or days' duration alternating with long periods of normal rhythm. When block was present the patient complained of weakness, faintness when upright and dyspnea on exertion, and he was nervous and apprehensive. On the resumption of normal rhythm these symptoms disappeared. During one of these attacks of block the cardiac output was estimated to be 10 cc per minute per pound of body weight, 56 per cent below the average normal. In normal rhythm the estimate was 18 and 21 cc on two occasions, both values being within normal limits.

We had a similar experience with a woman of 29 in whom hypertension had developed after a pregnancy. On admission to the hospital her blood pressure was 185 systolic and 140 diastolic or higher, her cardiac output was estimated to be below normal (17 cc per minute per pound of body weight) and her chief complaint was attacks of dizziness when upright. Four months later her blood pressure averaged about 150 systolic and 100 diastolic, her estimated cardiac output was within the normal limit (19 cc per minute) and she was no longer bothered by "spells."

Occurrence of the Cases—Patients with subnormal circulation are encountered frequently among those suffering from coronary heart disease and much less frequently among those with rheumatic heart disease. The majority of patients with hypertension without cardiac enlargement present this abnormality. Many instances have been found

among the older diabetic patients whose weakness and disability seemed out of all proportion to their metabolic defects. In our experience, most patients with very low metabolic rates and most patients with extremely small hearts have subnormal circulation. Indeed, the situation is so common that several cases are to be observed in the wards at almost any time.

The realization that subnormal circulation is characterized by a syndrome consisting of weakness, dyspnea on exertion and faintness in the upright position led to the search for instances of this condition wherever these symptoms were encountered. It soon occurred to us that this group of symptoms is characteristic of patients convalescent from the severe infectious diseases when they first leave their beds. Following this clue, we tested 5 patients convalescent from pneumonia and single patients after typhoid fever, tularemia, influenza and prolonged pyrexia of unknown origin. In all but 2 cases we estimated the circulation to be below the normal limit at this time. Figure 3 shows the ballistocardiograms of 3 such patients.

Among patients confined to bed and therefore not included in this series, subnormal circulation has been frequently encountered in association with congestive heart failure and with recent cardiac infarction, but it has not been found universally in association with either of these conditions.

Characteristic Symptoms Without Subnormal Circulation—As soon as it was realized that a definite syndrome characterizes many patients with subnormal resting circulations, we tested every patient exhibiting these symptoms, not only to add to the series but to ascertain whether the same symptoms would be encountered among patients whose circulation was normal. In a year's time 14 patients were encountered who complained of dizziness in the upright position or of attacks of fainting and whose circulation was within normal limits, at least on some occasions.

In 3 of these cases the cardiac output was just at the lower limit of normal, 18 cc per minute per pound. In 1 of these a second test yielded a subnormal value, and the discrepancy may have been due to excitement at the first test. Also, with inaccurate methods it is inevitable that a summation of errors would influence the results in some of the cases, and a sharp division between the normal and the abnormal cannot be expected.

In 3 other cases the patients had severe anemia. As the characteristic symptoms of dizziness and syncope are to be attributed to anemia of the brain, one would certainly expect anemic patients to show the same symptoms even though their circulation was normal.

Two of these patients had severe polycythemia. In 1 it was primary, in the other it was secondary to congenital heart disease.

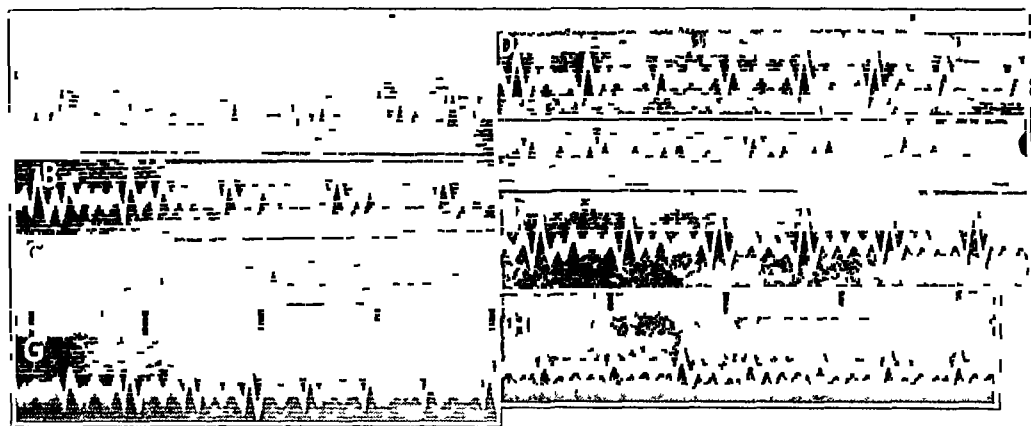


Fig 3—Ballistocardiograms (about one-third actual size) of patients with febrile diseases and during convalescence therefrom

A, record of M S, a woman aged 21, on November 15 (the fourth day of the disease) She was 5 feet (152.4 cm) in height and weighed 110 pounds (49.9 Kg) She had pneumonia of the bases of the lower lobe of the right and of the upper lobe of the left lung No pneumococci were cultured She had been given sulfapyridine for twenty-four hours The temperature was normal at the time of testing, it rose later in the day The patient was very weak The blood pressure was 130 systolic and 75 diastolic The cardiac output was 26 cc per minute per pound of body weight (difference from expected normal, +13 per cent) *B*, record of the same patient on November 22 She was convalescent Moist rales persisted in both sides of the chest The temperature had been normal for four days She was allowed out of bed for the first time The blood pressure was 110 systolic and 68 diastolic The cardiac output was 16 cc per minute per pound (—30 per cent) *C*, record of the same patient on November 28, immediately before discharge to her home The chest was almost clear, the patient still felt weak The blood pressure was 110 systolic and 60 diastolic The cardiac output was 18 cc per minute per pound (—22 per cent) *D*, record of E K, a woman aged 33, on October 13 (the thirtieth day of the disease) She was 5 feet 6 inches (167.6 cm) in height and weighed 115 pounds (52.1 Kg) She had had typhoid fever with relapse On the thirtieth day of the disease the temperature ranged from normal to 101 F The blood pressure was 120 systolic and 74 diastolic The cardiac output was 25 cc per minute per pound (+9 per cent) *E*, record of the same patient on October 30 She had been afebrile for thirteen days She had first been allowed to sit in a chair three days previously, she was still too weak and dizzy to walk without support The cardiac output was 17 cc per minute per pound (—26 per cent) *F*, record of the same patient on November 3 She was much stronger, was walking all over the ward and was ready for discharge The blood pressure was 120 systolic and 90 diastolic The cardiac output was 26 cc per minute per pound (+13 per cent) *G*, record of A G, a woman aged 23, on December 27 (the tenth day of a fever of unknown origin) She was 5 feet 2 inches (157.4 cm) in height and weighed 114½ pounds (52 Kg) The temperature was 104 F at the time of the test, the patient was prostrated The blood pressure was 92 systolic and 68 diastolic The cardiac output was 24 cc per minute per pound (+4 per cent) *H*, record of the same patient on January 2 She had been afebrile for four days She was much stronger but was not yet allowed out of bed The blood pressure was 90 systolic and 70 diastolic The cardiac output was 15 cc per minute per pound (—35 per cent)

probably the tetralogy of Fallot. Increased viscosity of the blood, lack of proper aeration of blood in the lungs and intermingling of the circulation in the second case are the factors which might have prevented an adequate supply of oxygen to the brain, although the cardiac output was normal.

In 4 instances the explanation of the discrepancy was less obvious. Two of the 4 patients resembled persons with hyperthyroidism in appearance but had normal metabolic rates, this group will be discussed later. The remaining 2 had an unusual diminution of blood pressure in the erect posture, although not to the extent encountered in cases of true postural hypotension. To raise blood to the head not only an adequate general circulation but adequate vascular adjustments are necessary. A subnormal circulation would make the task of the peripheral vessels more difficult, but they might be equal to it, conversely, as is suggested in these cases, failure in the periphery alone would diminish the blood supply of the brain.

The final case is illustrated by figure 4. The patient had only one functioning carotid artery at the time we studied him. His symptoms, dizziness and repeated attacks of fainting fluctuated in most instances with the state of his resting circulation, which was far more labile than that of a healthy person. But, although his circulation was subnormal when he suffered most severely, he often complained of symptoms when our estimate was within the normal range, and the local fault seems a sufficient explanation for this. Severe cerebral arteriosclerosis might be expected to cause a similar state of affairs, but we have not yet encountered such a case.

We also encountered many patients whose symptoms had a superficial resemblance to the syndrome of subnormal circulation. Three patients with epilepsy, 3 with labyrinthine vertigo with tinnitus and a true sensation of rotating and 5 whose dizziness was associated not with position but with headache, nausea or definite neurotic manifestations, such as compulsion and claustrophobia, all had normal circulation.

Relation of Subnormal Circulation to Other Clinical Entities—The question will present itself to many readers. Do all these patients with subnormal circulation have heart disease? The answer is that many of them have severe heart disease but that in many more the heart is normal by all tests that can be applied to it. This should occasion no surprise. The heart does not fill itself by its own efforts, its filling is dependent on conditions in the peripheral circulation. If not properly supplied with blood, a normal heart is helpless to maintain normal circulation. Conversely, a diseased heart, by drawing on its reserves, may maintain normal circulation. Though often associated, weakness of the heart and failure of the circulation are entirely distinct physiologic

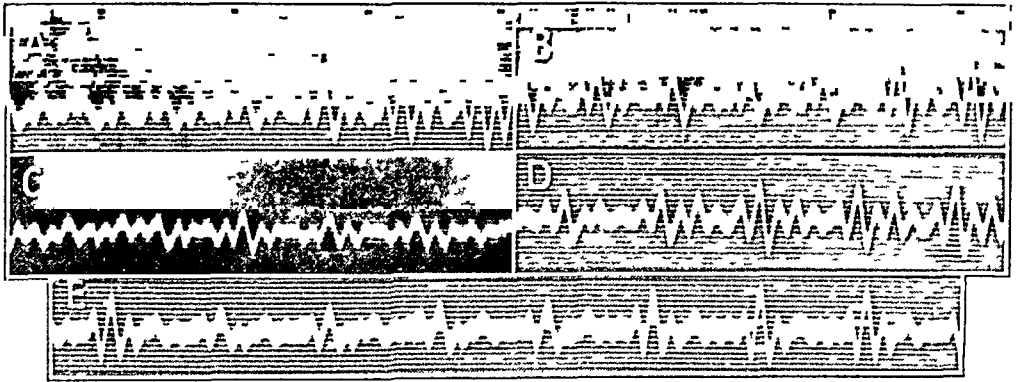


Fig 4—Ballistocardiograms of S B, an intelligent white storekeeper aged 50. His height was 5 feet 7 inches (170 cm), his weight, 143 pounds (64.9 Kg). He had had several fainting attacks a week for the past two years, becoming unconscious for periods ranging from fifteen seconds to one minute. There was no incontinence. He had also had frequent attacks of dizziness when upright, and these often led to syncope if he did not immediately lower his head. After demonstration that pressure on the right carotid sinus caused syncope, this sinus was denervated and, later, the right carotid bulb was removed. No improvement resulted.

Postoperative physical examination revealed no abnormality except moderate arteriosclerosis, slight hypertension and Horner's syndrome. The orthodiagram showed a heart silhouette 10 per cent below the expected normal. The value for blood sugar, determined repeatedly before and just after attacks, was always normal.

A, record of March 21, 1939. The blood pressure was 180 systolic and 85 diastolic. During the past two weeks he had fainted four times and had two attacks of dizziness. He was taking 5 mg of benzedrine and 10 grains (0.65 Gm) of tincture of belladonna twice a day. The cardiac output was 20 cc per minute per pound of body weight. *B*, record of April 4. The blood pressure was 180 systolic and 80 diastolic. He considered himself to be doing well. During the past two weeks he had not fainted at all and had only two attacks of dizziness. Medication was continued as before. The cardiac output was 25 cc per minute per pound. *C*, record of May 9, after an extremely bad week the blood pressure was 165 systolic and 95 diastolic. He had fainted, struck his head, been unconscious for longer than usual and had severe headache afterward. He also had repeated attacks of dizziness whenever he tried to get about. These were so bad that he remained in bed almost all week and reached the hospital only with the help of his wife. All medication was stopped. The cardiac output was 14 cc per minute per pound. *D*, record of May 23. The blood pressure was 150 systolic and 98 diastolic. The patient felt much better. There had been no dizziness or fainting for the past week. He had fainted three times the week before. No medication was given. The cardiac output was 20 cc per minute per pound. *E*, record of Nov 28. The blood pressure was 160 systolic and 90 diastolic. He considered himself to be doing very well. He had fainted three times and had four attacks of dizziness in the past month, none occurring in the week preceding this test. No medication was given. The cardiac output was 24 cc per minute per pound.

entities, and one must never be inferred from the presence of the other.¹⁰ In our patients without heart disease the fault should be sought in the peripheral circulation or in the volume of the blood.

Another question presents itself. With the tendency toward low basal metabolic rates, did these patients have primary thyroid deficiency? Patients with myxedema have subnormal circulation, and our patients who had had partial thyroidectomies doubtless fall into this group. But if the trouble were primarily in the circulation it would surely be to the advantage of the patient to reduce his metabolic rate. That such a reduction might be secondary to heart disease was first suggested to us by the discovery of extremely low metabolic rates in 2 cases of prolonged heart block,^{3a} and Stewart and his co-workers,¹¹ reporting another instance, have reached the same conclusion. The following case is most easily explained from that viewpoint.

REPORT OF A CASE

B. H., a woman 50 years of age, came to the hospital in 1937 with a three year history of typical angina pectoris after effort. Physical examination showed cardiac enlargement but nothing else of importance. An orthodiagram showed the heart silhouette to be 45 per cent above the predicted normal. The electrocardiogram (limb leads only) was essentially normal.

After six months' attendance at the outpatient department an appearance suggestive of myxedema was first noted. Increasing symptoms led to the patient's admission to the hospital two months later. There she presented the typical signs and symptoms of myxedema. The basal metabolic rate was -39 per cent. The electrocardiogram from chest leads suggested a former anterior infarction. On two occasions the cardiac output by the ballistocardiogram was 13 and 15 cc per minute per pound of body weight, 43 per cent and 35 per cent respectively below the expected normal.

With small doses of thyroid the symptoms improved, and the basal metabolic rate was -24 per cent on her discharge to the outpatient department, where she continued to receive thyroid. On March 18 her cardiac output was approximately 18 cc per minute, 22 per cent below normal, but extrasystoles replaced every second or third beat. On March 21 the basal metabolic rate was $+10$ per cent. Six days later she was discovered in collapse in her home and was rushed to the hospital. The blood pressure could not be obtained. The electrocardiogram showed tachycardia, the rate being 125, with a multitude of auricular extrasystoles, it gave no evidence of recent infarction. She died in a few hours. Necropsy was limited to the heart. There were an old infarct, 3 by 2 cm in the anterior

10 Starr, I. Failure of the Heart vs Weakness of the Circulation, in Symposium on the Blood, Heart and Circulation, Washington, D. C., American Association for the Advancement of Science, 1940.

11 Stewart, H. J., Detrick, J. E., Crane, N. F., and Thompson, W. P. Studies of Circulation in Presence of Abnormal Cardiac Rhythms. Observations Relating to Rhythms Associated with Rapid Ventricular Rate and to Rhythms Associated with Slow Ventricular Rate, *J. Clin. Investigation* **17** 449-463 (July) 1938.

portion of the left ventricle and another, 3 cm in circumference, in the inter-ventricular septum. Microscopic examination showed that both infarcts were extensively encroached on by scar tissue.

The cardiac lesion clearly antedated the myxedema in this case, and restoration of the basal metabolic rate to normal was followed by disaster. Therefore we are not prepared to regard thyroid disease as the primary cause of a lowered basal metabolic rate in every case. Besides the patient just described, none of our patients gave any of the clinical signs of myxedema, on the contrary, they seemed very alert.

Particular interest attaches to the group of patients having what is commonly known as "functional heart disease," because they suffer from many symptoms despite the fact that routine hospital procedures disclose nothing abnormal. Estimations of cardiac output disclose a profound physiologic abnormality in many of these cases, and the evidence at hand suggests that more than one pathologic situation is present. The ballistocardiograms of 2 patients with somewhat similar symptoms are shown in figure 5. Both of these patients might properly have been considered

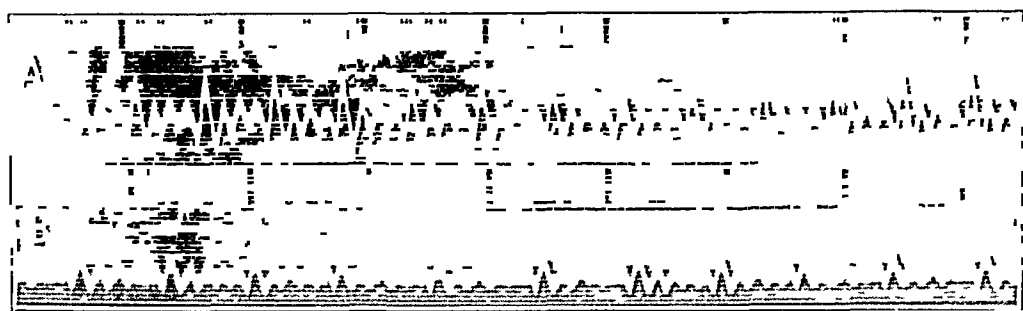


Fig 5—Records of contrasting conditions, both of which might be diagnosed as functional heart disease. The records are one-half actual size.

A, record of A W, a housewife aged 27, weighing about 106 pounds (48.1 Kg). She had been coming to the outpatient department for six years. Her complaints were nervousness, palpitation, dyspnea on exertion and dizziness. She suffered from attacks of precordial discomfort usually associated with palpitation and dizziness. These attacks did not necessarily follow exertion and sometimes occurred when she was in bed. Physical examination showed the facies suggestive of hyperthyroidism. She had slight exophthalmos and slight tremor, and she was constantly fidgeting. She had no goiter. Six estimates of the basal metabolic rate were normal, the last two were -2 and -1 per cent of normal, respectively. The resting cardiac output was 29 cc per minute per pound of body weight, 26 per cent above the average normal, the pulse rate being 108. B, record of G A G, a school teacher aged 33, weighing 92 pounds (41.7 Kg). Her troubles had begun three years previously. The complaints were weakness and easy fatigability, dyspnea on exertion, dizziness and light headedness when upright. She also had crying spells, during which she had palpitation and precordial distress. She suffered from "gastric distention" and belching. Physical examination showed nothing abnormal. The size of the heart was normal by the fluoroscope. The basal metabolic rate was -10 per cent. The resting cardiac output was 15 cc per minute per pound, 35 per cent below the average normal, the pulse rate being 80.

to have "functional heart disease," and a psychiatrist diagnosed the condition of both as "anxiety neurosis," but the difference between the circulation of these patients is very striking, and it seems typical of the two groups they represent. To designate the condition of the group with subnormal circulation the term neurocirculatory asthenia fits perfectly, for the patients are weak, and they have symptoms referable to their circulation. We have encountered a smaller number of patients of the other type, but their appearance was very different. They were probably similar to the 2 patients described by Lequime¹² as having "parabasedowism," for their condition resembled hyperthyroidism so closely that only after repeated estimations of the basal metabolic rate was this diagnosis abandoned. Also, the dizziness of which some of them complained bore less relation to the upright position than in the patients with subnormal circulation. Drugs of the epinephrine series, such as benzedrine, given to certain of the patients with small circulations caused symptomatic improvement. Epinephrine itself given to a number of patients with supernormal circulation reproduced the symptoms of which they commonly complained.

The belief that such dizziness and attacks of fainting as were shown by so many of our group can be attributed to subnormal circulation is an old one. A very clear statement of this view was given by Cotton and Lewis,¹³ who discussed fainting attacks they had observed in young soldiers. They said

Of the predisposing causes of fainting we know little beyond the frequent association of fainting and the condition termed "irritable heart." In cases which suffer from "irritable heart" giddiness, transient or enduring, is the rule rather than the exception. Change of posture is the chief exciting cause. The loss of consciousness is clearly to be sought in anemia of the brain, and this anemia is provoked by the combination of two factors, lowered heart rate and lowered force of beat.

Our view differs from that of these authors in certain respects. Our evidence suggests that the subnormal general circulation is the predisposing cause in such cases and that the vagal stimulation to which they attributed the attacks may occur late in the development of symptoms¹⁴ and so be a result, rather than a cause, of the diminished cerebral circulation. But it seems evident that when the general circulation is subnormal the physiologic problem of maintaining an adequate blood supply

12 Lequime, J. *Le debit cardiaque, etudes experimentales et cliniques*, Paris, Masson & Cie, 1940.

13 Cotton, T. F., and Lewis, T. *Observations upon Fainting Attacks Due to Inhibitory Cardiac Impulses*, *Heart* 7:23, 1918.

14 Starr, I., and Collins, L. H., Jr. *Physiological Studies of Faintness and Syncope*, *J. Clin. Investigation* 9:561-577 (Feb.) 1931. Weiss, S., Wilkins, R. W., and Haynes, F. W. *The Nature of Circulatory Collapse Induced by Sodium Nitrite*, *ibid.* 16:73-85 (Jan.) 1937.

to the brain is rendered far more difficult and that this defect would make these patients subject to attacks of fainting whenever reflex or endocrine influences upset the vascular adjustments

Our results have changed our view of the Stokes-Adams attack so frequent in cases of heart block. These attacks of fainting have been generally attributed to asystole coincident with a change in the cardiac rhythm, and this may be the precipitating mechanism in some instances. But syncope has occurred frequently in our patients who appeared constantly to have heart block. In such cases we now regard these attacks of fainting as analogous to those which so frequently accompany a subnormal circulation from any cause. It is in cases of heart block that some of the most subnormal circulations have been found.

SUMMARY

From an analysis of the data obtained from a study of 100 ambulatory patients with subnormal cardiac outputs, the clinical characteristics of this group are described.

The majority of these patients are weak and easily fatigued, consider themselves unduly short of breath on exertion and often are nervous. The most characteristic symptom is attacks of dizziness, or light headedness, in the upright position, and many suffer from repeated attacks of syncope. The pulse rate, the size of the heart and the basal metabolic rate are most frequently in the lower half of the normal range, but in some cases they are definitely subnormal.

Ambulatory patients with subnormal circulation are common, and one or more of such patients are usually present in the medical wards. This abnormality occurs in about half of the patients with coronary heart disease, in valvular heart disease it is found much less frequently. It is common in patients with hypertension whose hearts have not enlarged, in patients with the indefinite condition usually termed neuro-circulatory asthenia, in patients with certain endocrine diseases and in convalescents from the severe acute infections.

The syndrome presented by these patients is definite enough to permit one to make the diagnosis in many instances when methods of measuring cardiac output are not available.

Progress in Internal Medicine

SYPHILIS

REVIEW OF THE RECENT LITERATURE

CHARLES F MOHR, M D

PAUL PADGET, M D

AND

JOSEPH EARLE MOORE, M D

BALTIMORE

The material for this article has been selected mainly from publications which have appeared from July 1939 to July 1940. As in previous reviews,¹ it has been necessary rigidly to select material. Little attention has been paid to reports dealing with comparative serologic studies, and case reports have been almost wholly eliminated.

HISTORY OF SYPHILIS

Peter Kalm, a Swedish botanist, began a tour of North America in September 1748 and in 1750 published from his observations a treatise entitled (in translation) "Lobelia as a Sure Cure for Venereal Disease." With prefatory comment to identify Peter Kalm, Larsen² provides an interesting translation of his treatise.

The American savages in the northern part of America have had *lues Venerea* among them for a long time past. Some say that the Europeans brought the disease to the savages, others claim the disease was present among them much earlier.

In spite of the fact that quicksilver is unknown to them, the savages consider this disease one of the easiest to cure by the use of certain herbs. All accounts agree that it is impossible to get the savages to reveal the remedy. They keep it secret, for they have the superstition that if they reveal to any European the remedy, it will, from that time, lose its value.

From the Syphilis Division of the Medical Clinic, the Johns Hopkins University and Hospital.

1 (a) Moore, J. E. Syphilis. A Review of the Recent Literature, *Arch Int Med* **56** 1015 (Nov) 1935. (b) Padget, P., and Moore, J. E. Syphilis. A Review of the Recent Literature, *ibid* **58** 901 (Nov) 1936, (c) **60** 887 (Nov) 1937. (d) Padget, P., Sullivan, M., and Moore, J. E. Syphilis. A Review of the Recent Literature *ibid* **62** 1029 (Dec) 1938. (e) Moore, J. E., and Mohr, C. F. Syphilis. A Review of the Recent Literature, *ibid* **64** 1053 (Nov) 1939.

2 Larsen, E. L. Lobelia as a Sure Cure for Venereal Disease, *Am J Syph, Gonorr. & Ven. Dis* **24** 13 (Jan) 1940.

Colonel William Johnson³ lives among the savages and has in many ways gained their respect and love. No one is more familiar with their mode of life. He told me that, with unbelievable ease, they cure venereal disease by means of herbs.

[Here Kalm details his conclusion that only Colonel Johnson could learn the secret, and the methods he suggested to this officer for approaching the problem and continues.]

I will not discuss the trouble, expense, and persuasive arguments used by this gentleman in order to learn the secret. As a result three savage women showed him the same herb and gave him similar accounts of the use of the remedy.

The herb was a species of *Lobelia*, further identification Kalm dismissed by saying that, after all, he couldn't carry a botanic library around in such primitive country. It was probably either *Lobelia siphilitica* or *Lobelia inflata* (Indian tobacco). It is interesting that of the latter astute old Asa Gray⁴ said, "Plant a noted quack medicine."

The technic of treatment was involved and rigorous, but the results

Cures as complete are effected by herbs as have ever been effected by quicksilver. The chief difference is this: that one need never fear of losing one's life by the savages' remedy. A case cannot be found of a savage who has died of this disease, who died during the treatment, a case of a patient not cured cannot be found. Those who have been so unfortunate as to have tried both the quicksilver remedy and that of herbs say that the herb remedy is much milder and better.

Zimmermann⁵ has translated Joseph Grunpeck's "*Libellus de Mentulagra alias Morbo Gallico*." This worthy was not a physician, and his treatise is of interest as an accurate description of his own infection at a time when good clinical descriptions of disease are almost wholly lacking. He felt that the treatment of the day was barbarous, for him it was certainly ineffectual, so after the second relapse he decided to study the disease and treat himself. His plan of treatment involved blood letting and selective medication, for one phase of which he recommended the following syrup:

℞ 1½ handfuls each of endive, hepatica, hops, maidenhair, bugloss, borage and sorrel, 1 handful each of wormwood, fumitory and sage, 1 dr each of flowers of violets, red roses, borage and bugloss, 1½ oz each of cleaned barley, grated liquorice and barberries, 1 oz of cleaned raisins, ½ oz each of senna, dodder and polypody, 1 dr each of seeds of anise, fennel and parsley. Which, macerated and boiled down in 8 lb of water to ⅔ volume, is allowed to stand 4 hr. To the

3 Sir William Johnson, Colonial Superintendent of Indian affairs.

4 Robinson, B. L., and Fernald, M. L., in Gray, A. New Manual of Botany, ed 7, New York, American Book Company, 1908, p 769.

5 Zimmermann, E. L. Joseph Grunpeck's *Libellus de Mentulagra Alias Morbo Gallico* of 1503, *Am J Syph, Gonorr & Ven Dis* 24:364 (May) 1940.

expressed fluid is added 1 lb of sugar or honey It is then boiled a second time and strained This syrup thoroughly depurated and freed of dregs, will crush the pride of the enemy within the intestines, the pestiferous poison of the disease

In an interesting study of the early epidemics of syphilis, Rosenthal⁶ points out that without modern knowledge of the nature of the infection and the mode of transmission, the epidemics of syphilis which swept Europe in the sixteenth and seventeenth centuries appeared to be supernatural visitations and were attributed to various causes Apparently the disease would spring up in a new community by spontaneous generation, and so it became known under many names, most of which were derived from the localities of the earlier epidemic Many of the descriptions, however, were amazingly accurate, not only as to clinical symptoms, but also in the clear conception of the means of transmission of the disease which they reflected For instance, in 1646 Governor John Winthrop of the Massachusetts colony reported an outbreak of syphilis in Boston, saying "And it was observed that although many did eat and drink and lodge in bed with those who were infected and had sores, etc , yet none took it of them, but by copulation or sucking "

One of the earliest epidemics occurred in 1578 in Brunn, Moravia, and was ascribed to a barber, who made scarifications with a dirty razor , this epidemic was called the morbus brunno-gallicus The disease was reported from Amboina under the name of Amboina pustules in 1718, as radesyge from Norway and Sweden in 1720 , as the disease of Sainte Euphémie, whence it had been introduced by a midwife, in 1727 In 1752 an epidemic among infants apparently infected by wetnurses was described under the name of *pian de Nérac*, and by 1770 an epidemic of the disease was reported from Scotland under the name of sibbens or sivvens

Syphilis apparently reached Canada between 1776 and 1780, where it was first designated the disease of the Bay of Saint Paul, because of its frequency in that region , later it became known as *le mal de chucot*, *le mal des éboulements* and Ottawa disease From this point, reports of localized epidemics became more frequent as the disease spread and was more frequently recognized , thus, there was the epidemic in the village of Facaldo in 1876, in Dithmarschen and eventually elsewhere in Holstein in 1789, Courland in 1800, Fiume in 1800, Chavanne in 1816, Jutland in 1817 and Capistrello in 1859 Of especial interest is the Cracow episode of 1805, when there was an epidemic of syphilis among newborn Jewish boys Investigation revealed that the official assigned to draw blood with his lips at the ritual of circumcision had syphilitic lesions in his mouth

6 Rosenthal, T Old Epidemics of Syphilis, Arch Dermat & Syph 40 59 (July) 1939

Melikian⁷ says that the diseases *wuk* and *godutin* which are described in the Armenian manuscripts of the fourth century must have been syphilis and that the introduction of the disease into Spain was by the Arabs. Hamlin⁸ presents maps to show geographically how spirochetal diseases might have spread to Europe from the New World.

SPIROCHAETA PALLIDA

Staining—Efforts continue to devise a simple method for staining *S. pallida*, which can be used either by the physician or in a central laboratory, to obviate the necessity for immediate dark field examination of material from a lesion suspected to be primary syphilis. Knisely⁹ calls attention to a colloidal aqueous solution of silver (known commercially as collargolum), which he has found to be highly successful for the purpose and to check consistently with direct dark field examination of the same material. Nagle and Graul¹⁰ report high agreement between the nigrosin stain and direct dark field examination. To the same end, Krajian¹¹ again mentions the method which he has previously described,¹⁶ which is designed for biopsy specimens.

Knisely⁹ makes the point that a stained smear in which morphologically typical spirochetes are present constitutes a valuable permanent record which may be filed for future reference. He does not suggest, but the conclusion is obvious, that in well ordered practice the discovery of *S. pallida* by dark field examination should be the occasion for embalming a stained smear. Otherwise, the advantage of the staining methods is dubious.

Steiner¹² describes in detail a silver impregnation method for staining spirochetes in paraffin sections of tissue, of which he says

The method herein described for staining spirochetes in paraffin sections is at least equal in its effects to other commonly used methods of staining spirochetes. The Levaditi, Noguchi, and Jahnke methods are silver salt reduction methods.

7 Melikian, O. Ueber den Ursprung der Syphilis, München med. Wchnschr. **86** 1167 (July 28) 1939.

8 Hamlin, H. The Geography of Treponematoses, Yale J. Biol. & Med. **12** 29 (Oct.) 1939.

9 Knisely, M. J. A Simple and Time-Saving Procedure for the Identification of Treponema Pallidum, J. Lab. & Clin. Med. **24** 1309 (Sept.) 1939.

10 Nagle, N., and Graul, J. Dark Field Examination and Nigrosin Stain in Demonstrating Treponema Pallidum, J. Lab. & Clin. Med. **25** 660 (March) 1940.

11 Krajian, A. A. The Clinical Application of a Twenty-Minute Staining Method for Spirochaeta Pallida in Tissue Sections, Am. J. Syph., Gonorr. & Ven. Dis. **23** 617 (Sept.) 1939.

12 Steiner, G. A. Simple Method of Staining Spirochetes in Routine Paraffin Sections, with Remarks Regarding Distribution of Spirochetes in Tissues, J. Lab. & Clin. Med. **25** 204 (Nov.) 1939.

which can be used only on tissue blocks. The Warthin-Starry and Dieterle methods may be useful for paraffin sections, but they are more complicated or take longer than this method.

Distribution of Spirochetes in Tissue—According to Steiner,¹³ in active syphilis spirochetes occur in "conglomerations," i. e., densely clustered masses containing large numbers of the organisms. These, he thinks, represent reproduction centers.

Sahyoun¹⁴ studied sections of placentas from syphilitic women which had been stained by a special differential technic. Using similarly stained sections from sciotal syphilomas of rabbits for comparison, he concluded that the spirochete-like objects stained in the syphilitic placenta were not elastic or collagen fibers, reticular fibrils, fibrin, fibrinoid material or cell boundaries. He concludes, therefore, that the observed structures are spirochetes.

Culture—Attempting to grow the T1uffi strain of *S. pallida* on the chorio-allantoic membrane of the chick embryo, Sterzi and Staudacher¹⁵ found that the organisms migrated from transplants of syphilitic tissue in a regular and progressive manner, to be found 1 cm. from the transplant in one hour, 2 cm. in two hours and 4 cm. after six hours. No multiplication appeared to occur, and after twenty-four hours the spirochetes in the chorio-allantoic membrane lost their motility but did not change morphologically. Those in the inoculating transplant showed morphologic changes in eight to fourteen hours. The development of the embryo was not affected.

Mason¹⁶ inoculated material from 58 chancres and 2 condylomata lata into fifteen different culture mediums. The exact procedure is difficult to follow, but of these only coagulated horse serum, coagulated ascitic fluid and a modification of the Zinsser-Hopkins medium would maintain spirochetes. However, the resulting cultures proved to be avirulent for rabbits.

In a vague article with few details Grigorev¹⁷ claims the culture of pathogenic *S. pallida*, by inoculating Tarozzi's medium with the blood of patients with early syphilis. He is entirely unconvincing.

13 Steiner, G. A. Morphologic Appearances of Spirochetal Reproduction in Tissues, *Arch. Path.* **29** 189 (Feb.) 1940.

14 Sahyoun, P. F. The Differentiation Between Spirochetes and Spirochete-Like Structures in the Placenta, *Am. J. Path.* **15** 455 (July) 1939.

15 Sterzi, G., and Staudacher, V. Tentativi di coltura della spirocheta di Schaudinn sulla membrana corionallantoidea di embrione di pollo vivente, *Gior. ital. di dermat. e sif.* **80** 777 (Aug.) 1939.

16 Mason, H. C. Avirulence of Culture Spirocheta Pallida, *Urol. & Cutan. Rev.* **43** 733 (Nov.) 1939.

17 Grigorev, P. S. About the Pathogenicity of Pure Cultures of Spirocheta Pallida. *Acta med. URSS* **2** 361, 1939.

Turner and Fleming¹⁸ demonstrated that spirochetes and filtrable viruses remained virulent for as long as three years if stored at -78°C (-108.4°F)

S. Pallida in Blood in Early Syphilis—Frazier and Pian¹⁹ report an interesting case to show that in man, as in the experimental animal, invasion of the blood stream by *S. pallida* takes place before the primary lesion develops

A child 8 years old was the recipient of a blood transfusion. Both at the time and repeatedly previously the donor's blood had given negative results to serologic tests for syphilis. Twenty days later the donor appeared with a chancre, dark field examination of material from which revealed *S. pallida*. Serologic tests for syphilis gave positive results. In the recipient secondary syphilis and a fulminating syphilitic osteomyelitis developed. Serologic tests for syphilis gave positive results, and in 1 of 4 rabbits there developed typical syphilitic orchitis with *S. pallida* to be demonstrated in the testicular fluid, following the intratesticular injection of 1 cc of the child's blood seventy-eight days after the transfusion.

The fact that serologic tests for syphilis gave positive results at the time the donor's chancre was recognized tends to discount the implication that the lesion had just appeared. It apparently was not present at the time of the transfusion, however, so the authors present the situation as evidence that spirochetemia precedes the development of the primary lesion of syphilis in man.

EXPERIMENTAL SYPHILIS

Effect of Sex Hormones on Experimental Syphilis—Pursuing their studies on the effect of sex and of sex hormones on the behavior of experimental syphilis in the rabbit, Kemp, Shaw and Fitzgerald²⁰ investigated the effects of testosterone propionate.

In a study of the effect of the male sex hormones upon the course of experimental rabbit syphilis, 5 mg of testosterone propionate were administered intramuscularly to 42 rabbits for four weeks before and eight weeks after inoculation with the Nichols strain of *T. pallidum*. The animals included in the experiments

18 Turner, T. B., and Fleming, W. L. Prolonged Maintenance of Spirochetes and Filterable Viruses in the Frozen State, *J. Exper. Med.* **70**: 629 (Dec.) 1939.

19 Frazier, C. N., and Pian, H. C. Isolation of *Treponema Pallidum* from Blood During Primary Incubation Period of Human Syphilis, *Chinese M. J.* **56**: 441 (Nov.) 1939.

20 Kemp, J. E., Shaw, C., and Fitzgerald, E. M. The Effect of Testosterone Propionate on the Course of Experimental Rabbit Syphilis, *Am. J. Syph., Gonorr. & Ven. Dis.* **23**: 430 (July) 1939.

were divided into five groups (1) castrated males treated with testosterone, (2) normal males treated with testosterone, (3) normal females treated with testosterone, (4) untreated males, (5) normal untreated females. Seventy-one animals divided approximately equally between the experimental and control groups survived the experiment.

It was found that

As judged by the average maximum size of the chancres which developed at the site of inoculation and the frequency of generalized lesions treated noncastrated males reacted more severely to infection than normal males.

The behavior to infection of castrated males treated with testosterone and of normal males and normal females was approximately the same.

As judged by the frequency with which generalized lesions were encountered, treated female rabbits, none of which showed evidence of generalization, reacted less severely than any of the experimental or control groups.

A surprising finding was the almost parallel reaction to infection of the male and female control animals.

From his experiments, Hu²¹ concludes that estrogen exerts an inhibitory influence on the course of syphilitic infection in the rabbit, but that it alone is not responsible for all the difference in severity of the infection between the sexes.

Immunity in Syphilis—Following Turner's^{1e} demonstration of the humoral component of the immunity in rabbits with syphilis, Turner, Fleming and Brayton²² show that a similar protective antibody is present in the serum of human beings with the disease.

"Protection" tests were made with serum of 80 persons according to the technic previously described. Sixty of these people had syphilis (11 had achieved seronegativity), and there were 20 nonsyphilitic controls. In 53 of the former, serums showed definite evidence of protection, in 4 the results were equivocal, and in 3 there was no evidence of protective antibodies by this experimental technic. Sixteen of the 20 specimens of serum from nonsyphilitic persons showed no evidence of protection, 2 yielded results which were equivocal, and 2 showed definite protection. The serum of 10 of the 11 syphilitic persons with negative reactions to serologic tests for syphilis contained protective antibodies.

Experimental Fever Therapy—Yata²³ treated syphilitic rabbits by means of the radiotherm, the heat cabinet and inoculation with rat bite fever spirochetes.

21 Hu, C K. Lowered Resistance to Syphilitic Infection in Ovariectomized Rabbits, *Am J Syph, Gonorr & Ven Dis* **23** 446 (July) 1939.

22 Turner, T B, Fleming, W L, and Brayton, N L. Protective Antibodies in the Serum of Human Syphilitics, *J Clin Investigation* **18** 471 (July) 1939.

23 Yata, T. Experimental Studies on Fever Therapy of Syphilis, *J Exper Med* **17** 463 (Dec 20) 1939.

The immediate results were identical in the three groups of 19, 18 and 20 rabbits respectively, the testicular syphilomas retrogressed, and the serologic tests for syphilis fell in titer. Relapse and the development of metastases occurred conspicuously less frequently, however, among the group which had received intensive treatment by radiotherm, but organ transfer experiments showed that even the rabbits which remained asymptomatic were not cured.

Tuberculosis in Syphilitic Rabbits—Aronson and Meranze²⁴ previously have shown that untreated syphilitic rabbits react differently from nonsyphilitic rabbits to the intracutaneous injection of living virulent tubercle bacilli. The local reaction appears earlier in the former and is more intense, focal in character and particularly distributed about the capillaries. In the present communication, the authors²⁴ describe the reaction of treated syphilitic rabbits to the same maneuver. Six weeks after intratesticular inoculation with the Nichols strain of *S. pallida*, 12 rabbits of the same breed were given intravenously 20 mg of arsphenamine per kilogram of body weight. A week later half this dose was repeated. Three weeks after the second arsphenamine treatment, 0.1 mg in 0.1 cc of sodium chloride solution of the same strain of tubercle bacilli used in the first study was injected in six areas of the skin of the abdomen. As before, sites of injection were removed for study at intervals ranging from one hour to fourteen weeks. They found that the gross and microscopic lesions in these treated syphilitic rabbits did not differ conspicuously from the lesion observed in untreated syphilitic rabbits.

Laboratory Animals—Bessemans and de Moor²⁵ have concerned themselves with the susceptibility of small laboratory animals to infection with *S. pallida* and *Spirochaeta cuniculi*. Working with the rabbit, guinea pig, white mouse, white rat, common hamster, golden hamster, hedge hog, large rat and domestic mouse, the authors particularly have attempted to determine susceptibility, the incubation period of the infection, the distribution of spirochetes in the various organs of the body and contrasts between demonstration of *S. pallida* by dark field examination and proved infectiousness of organs by transfer experiments. Perhaps of greatest interest was the observation that the golden hamster was readily to be infected with *S. pallida* but not with *S. cuniculi* and that the organisms were plentiful in the various tissues, including those of

24 Aronson, J. D., and Meranze, D. R. Effect of Antisyphilitic Treatment on Histopathology of Local Tuberculous Lesions in Syphilitic Rabbits, *Proc. Soc. Exper. Biol. & Med.* **43**: 83 (Jan.) 1940.

25 Bessemans, A., and de Moor, A. Réceptivité des petits animaux de laboratoire à la syphilis et à la pallidoidose, *Ann. Inst. Pasteur* **63**: 569 (Dec.) 1939.

the spleen and brain The authors urge, therefore, further use of this animal in the study of experimental syphilis

Serologic Tests in Syphilitic Mice—Utilizing the Eagle microflocculation test, Fitzgerald, Shepherd and Kemp²⁶ followed the serologic reactions in 57 white mice which had been inoculated with material from testicular syphilomas of rabbits Their findings confirmed the observation of other workers that serologic tests for syphilis infrequently give positive results under these circumstances and therefore are of no value in studying the course of experimental syphilis in this animal

SERODIAGNOSIS OF SYPHILIS

Serologic Surveys—The Committee for the Evaluation of Serodiagnostic Tests for Syphilis²⁷ compares the results of the serologic survey made in 1938 with results of that conducted in 1939 Competing in the 1938 survey were forty-six laboratories, representing forty-four states and the District of Columbia, in the 1939 survey thirty-eight state and three Public Health Service laboratories participated The 1939 survey shows a definite improvement in the performance of the various state laboratories

In a contribution which is of interest in view of the increasing use of the serologic dragnet Ledgerwood²⁸ says

In serodiagnostic surveys of the prevalence of syphilis it has been customary to assume that the number of positive reactions obtained in a given group roughly corresponds to the number of infected cases in the group It can be shown, however, that the correspondence of infections to positive reactions depends entirely on the particular test employed The same number of positive reports given by two tests may be evidence of a widely different number of infections and two diverse reports given by two tests may be indicative of an identical prevalence Under certain circumstances, the number of infections which can be deduced from the number of positive reports is completely indeterminate, that is, a given result may be indicative of any number of cases of infection

Documentation is provided by Ledgerwood's statistical analysis of the results of the surveys reported by the Committee for the Evaluation of Serodiagnostic Tests for Syphilis^{1a}

Suppose that in one survey of a population of 100,000 individuals, 5,287 positive tests are reported Suppose that in the survey of a second population

26 Fitzgerald, E M , Shepherd, M , and Kemp, J E Microflocculation Test of Eagle in Syphilitic White Mice, Proc Soc Exper Biol & Med **42** 427 (Nov) 1939

27 Hazen, H H , Parran, T , Mahoney, J F , Sanford, A H , Senear, F E , Simpson, W M , and Vonderlehr, R A Serodiagnostic Tests for Syphilis as Performed in State Laboratories in 1938 and 1939, Ven Dis Inform **21** 171 (June) 1940

28 Ledgerwood, R Statistical Studies of Serologic Surveys, Am J Syph, Gonorr & Ven Dis **24** 284 (May) 1940

of 100,000 individuals another test yields exactly the same number of positive results. A few elementary considerations will suffice to show that the number of actual infections indicated by the one test may be substantially different from that indicated by the other.

To illustrate [] A test performed by Ruediger attained a sensitivity of 88.2 per cent and a specificity of 97.8 per cent. In the same series

the Kahn standard diagnostic test performed by its originator attained a sensitivity of 80.5 per cent and a specificity of 99.8 per cent.

In what kind of a population of 100,000 individuals may Ruediger's test be expected to show 5,287 positive reactions? Only in a population containing 3,590 infections.

When we turn to Kahn's test, we find that [it] could return 5,287 positive reports only in a population containing 6,335 actual infections.

Quantitative Serologic Tests—Kahn²⁹ suggests that the routine use of a quantitative serologic test for syphilis may be an aid to both diagnosis and treatment of the disease. He provides no evidence but thinks that accumulated experience indicates that quantitative tests have some (perhaps large) as yet undetermined value in following a patient under *treatment* and particularly in the post-treatment follow-up of those who manifest seroresistance. His estimate of the value of a single quantitative serologic test in the *diagnosis* of syphilis, however, is rather optimistic, and there is as yet no evidence to substantiate his statement that "low, moderate, and high titres correspond in most instances, to low, moderate, and marked syphilitic activity."

Culture Spirochetes as Antigen in Serologic Tests for Syphilis—The use of culture spirochetes as an antigen in the Wassermann reaction is not new. As is well known, efforts to grow pathogenic *S. pallida* on artificial mediums have so far failed, but many workers have grown a similar but nonpathogenic organism from which they prepared antigens for use in a serodiagnostic test for syphilis. Gaetgens,³⁰ however, was the first to obtain a sensitive complement fixation test by using a spirochetal antigen. The exact method for preparation of his antigen has not been published in duplicable detail, but the antigen is commercially available in Germany under the trade name of "palligen" and essentially is made by phenolizing cultures of the Reiter strain of the

29 Kahn, R. L. Facts Regarding the Quantitative Kahn Reaction, Ven Dis Inform **20** 255 (Sept) 1939.

30 Gaetgens, W. (a) Theoretisches und Praktisches über die Wirkung eines karbolisierten wässerigen Pallidaantigens, Ztschr f Immunitätsforsch u exper Therap **63** 398, 1929, (b) Weitere Erfahrungen über das wässrige karbolisierte Pallidaantigen für die serologischen Luesnachweis, Zentralbl f Bakt (Abt 1) **118** 26, 1930, (c) Weitere Untersuchungen über die Pallidareaktion, insbesondere ihre Beziehungen zur Wassermann, Ztschr f Immunitätsforsch u exper Therap **73** 527, 1932, (d) Die Pallidareaktion zum serologischen Luesnachweis, Med Welt **6** 765 (May 28) 1932, (e) Die bisherigen Erfahrungen mit der Pallidareaktion zum serologischen Luesnachweis, Arch f Dermat u Syph **176** 42, 1937.

spirochete In the past eleven years there have been numerous reports in the Continental literature regarding this "pallida reaction," but its reported sensitivity was so far below that of the better American serologic tests that it attracted little attention in this country It now appears that this low sensitivity was not the fault of the spirochetal antigen but lay principally in the basic technic of the test, and that "palligen" makes a satisfactory and perhaps superior antigen when used in a standardized complement fixation reaction Schleif³¹ found the pallida reaction to be more sensitive and slightly more specific than the Wassermann reaction and flocculation test with which he compared it Gartner³² agrees regarding sensitivity, but in his hands the pallida reaction gave more false positive results than the control tests Zundel³³ considers the pallida reaction as a valuable diagnostic aid if it is used in conjunction with standard complement fixation and flocculation tests but feels that syphilis should not be diagnosed on the basis of a positive pallida reaction alone, in the presence of otherwise negative serologic tests and clinical findings

Cappelli³⁴ performed the pallida reaction and standard serologic tests for syphilis on blood from 24 supposedly nonsyphilitic lepers The serum of only 1 patient gave a positive reaction with the spirochetal antigen, whereas 66 per cent of the serum reactions were positive with the Wassermann test and 39 per cent with the Meinel test It was later found that the 1 patient whose serum gave a positive reaction with the spirochetal antigen had syphilis

The first report on the pallida reaction in the American literature is by Erickson and Eagle,³⁵ who did complement fixation tests with a spirochetal antigen on 1,032 serum specimens, using the Eagle flocculation test and the Eagle modification of the Wassermann reaction as controls The serums were divided into two groups, 490 were from patients under treatment for syphilis, and 542 were from patients of a general dispensary and hospital population, who had given a negative

31 Schleif, L Erfahrungen mit der Pallidareaktion (nach Gaetgens) Diagnostische und Therapeutische Bedeutung, *Ztschr f Immunitätsforsch u exper Therap* **95** 431 (June 8) 1939

32 Gartner, H Die Pallidareaktion Ergebnisse aus zwei Jahren und Bemerkungen zu ihrer Technik, *Ztschr f Immunitätsforsch u exper Therap* **96** 225 (Aug 31) 1939

33 Zundel, W Die europäischen Epidermophytonpilze, *Arch f Dermat u Syph* **179** 120, 1939

34 Cappelli, E La "pallidareazione" di Gaetgens sui sierii lebbrosi, contributo allo studio dell'essenza della r Wassermann, *Gior di batteriol e immunol* **22** 425 (March) 1939

35 Erickson, P T, and Eagle, H An Evaluation of the Spirochete Complement Fixation Reaction in Comparison with the Eagle Flocculation and Wassermann Procedures, *Ven Dis Inform* **21** 31 (Feb) 1940

reaction to the Eagle flocculation test. Of the 490 serums from patients under treatment for syphilis, the spirochetal complement fixation technic detected 85 per cent, as compared with 68.5 per cent for the Eagle Wassermann test and 75.5 per cent for the Eagle microfloculation test. Among the other group there were 18 in whom the spirochetal complement fixation test gave a positive or doubtful reaction, while the control tests gave negative results. In 14 of these, further investigation revealed a history or clinical evidence of syphilis. In 2 of 88 samples of cerebrospinal fluid the spirochetal complement fixation tests gave positive results while those with the Wassermann test were negative. The history and clinical findings in one of these strongly suggested syphilis of the central nervous system.

The authors say

Despite the brilliant results obtained with the spirochetal reaction in the present preliminary study, confirming the previous reports from Germany and England, we as yet hesitate to recommend it as a routine diagnostic test unsupported by some other standard procedure. Primarily, this reservation is due to the excessively narrow range of concentrations over which the particular suspension here studied (palligen) can be used with safety. With the present technic, it was anticomplementary in dilutions of 1:2 to 1:3, and its reactivity was demonstrably weakened in dilutions higher than 1:10. The narrow useful range (1:6 to 1:8) is uncomfortably close to the anticomplementary zone and compares unfavorably with the extraordinarily wide range of safety available in properly prepared Wassermann antigens. The utmost care is necessary both in setting up controls and in reading and interpreting the results. A second lot of the spirochetal suspension purchased from the same source was far less reactive than the lot used in the present study, and had an even narrower margin of safety between the anticomplementary and reactive levels. Moreover, this killed suspension of spirochetes is a proprietary preparation. The manufacturers refuse either to divulge the details of its preparation or to make available living cultures of the organism (Reiter strain). Although attempts to produce equally reactive cultures from other strains of so-called *T. pallidum* (Noguchi, Nichols, Kroó) are now in progress, all the suspensions so far prepared in this laboratory have been too anticomplementary. Finally, since none of these cultured strains causes syphilis in susceptible experimental animals, none may actually be *T. pallidum*. When a pathogenic organism which is indubitably *T. pallidum* is finally cultivated, it may, and probably will, exceed any of these nonpathogenic strains in its reactivity with syphilitic serum.

Nevertheless, even in its present imperfect state, the spirochetal complement fixation test promises to point the way to the most significant advance in the sero-diagnosis of syphilis since the discovery of the Wassermann reaction. If its anticomplementary activity can be overcome, permitting the use of a more concentrated suspension, it may well be the method of choice.

In this connection, by means of absorption experiments with spirochetal antigen and beef heart antigen, Gaechtgens³⁶ has demonstrated the

³⁶ Gaechtgens, W. Ueber die antigene Wirkung von Pallidasuspensionen in karbolisierter Kochsalzlosung, *Med. Klin.* **25**: 390 (March 8) 1929.

existence of a specific antibody to the spirochete in syphilitic serums, separate from the antibody which reacts with beef heart lipoid Kroó, Schulze and Zander³⁷ express the belief that the two antibodies may be distinguished by the thermolability at 63 C (145.4 F) of the one which reacts with beef heart lipoid, while Hoeltzer and Ssuschkowa³⁸ could find no difference between the two Beck³⁹ contributes detailed studies on the nature of spirochetal antigens, and the summary of their own work, by Eagle and Hogan,⁴⁰ brings available information up to the moment

1 In confirmation of Gaehtgens, syphilitic human sera give positive complement fixation with cultures of so-called *T. pallidum* (Reiter strain) Syphilitic rabbit sera are equally reactive Syphilitic human and rabbit sera agglutinate these cultures, often in high titre (Beck)

2 Normal rabbit sera react weakly with the culture to give both agglutination and complement fixation in low titre Normal human sera, despite the fact that they contain agglutinins in low titre, fail to fix complement with the Reiter strain of cultured spirochetes Confirming Gaehtgens, the latter reaction is therefore of practical utility for the serum diagnosis of syphilis

3 When syphilitic serum is heated at 63° C, there is no demonstrable difference in the thermolability of the antibody to spirochetes, and of the reagin which determines the Wassermann and flocculation tests

4 (a) The absorption of syphilitic serum by spirochetal suspensions removes all reactivity, not only for the spirochetes, but for tissue lipoids (alcoholic beef heart extract) as well, the sera become Wassermann- and flocculation-negative (b) Absorption of syphilitic serum with tissue lipoids renders the Wassermann and flocculation tests negative, but does not demonstrably change the reactivity of the serum with spirochetes (c) Rabbits immunized to beef heart lipoid develop spirochetal agglutinins and complement-fixing antibodies (Reiter strain) in high titre

5 It is concluded that these cultured spirochetes contain antigenic material serologically related to a substance present in mammalian tissue, as well as other antigenic factors not present in such extracts, but equally reactive with syphilitic serum

These findings support the thesis that the primary serologic change in syphilis is the development of antibodies to *T. pallidum* The Wassermann and flocculation tests would be explained on the basis that the tissue extracts used as

37 Kroó, H, Schulze, F O, and Zander, I Untersuchungen uber die Immunitatsvorgange bei Syphilis, die syphilitische Blutveranderung, Klin Wchnschr 8 783 (April 23) 1929

38 Hoeltzer, R R, and Ssuschkowa, E G Zur Frage uber das Wesen der Wassermann-Reaktion, Ztschr f Immunitatsforsch u exper Therap 68 81, 1930

39 Beck, A The Role of the Spirochaete in the Wassermann Reaction, J Hyg 39 298 (May) 1939

40 Eagle, H, and Hogan, R B On the Presence in Syphilitic Serum of Antibodies to Spirochetes, Their Relation to So-Called Wassermann Reagin, and Their Significance for the Serodiagnosis of Syphilis, J Exper Med 71 215 (Feb) 1940

"antigen" in these tests contain one or more substances serologically related to antigenic components of *T pallidum*. Similarly, the cultured Reiter strain of spirochete is apparently sufficiently close serologically to *T pallidum* to be agglutinated by and to give complement fixation with the antibodies to *T pallidum* present in syphilitic serum.

Since suspensions of cultured spirochetes contain antigenic factors which react specifically with syphilitic serum, some of which are not present in ordinary Wassermann and flocculation "antigens," they may prove even more valuable than those tissue extracts in the serodiagnosis of syphilis.

Daily Variation in Serum Reagin—Mohr and Smith⁴¹ collected serum specimens at intervals of one to three weeks from patients with late syphilis who had been adequately treated and who were known to have given positive serologic tests for syphilis for a period of two or more years. A portion of each serum specimen was examined by quantitative technics in the routine serologic laboratory on the day it was collected, and the remainder of the specimen was frozen at -25°C (-13°F). When a sufficient number of specimens were collected from each patient, these were thawed and examined on the same day with the same reagents. In this way the authors sought to determine whether the apparent fluctuations in reagin titer which are observed in such patients were real or were manifestations of technical fluctuation in the laboratory.

They conclude

1 The daily variation frequently observed in the course of repeated serologic tests for syphilis on the same individual is not due to variations in the reagin content of the serum, but primarily reflects daily fluctuations in the sensitivity of the tests employed.

2 The daily fluctuations in the sensitivity of the tests proved to be greater with a Wassermann test than with a flocculation test, and disappear entirely when serum specimens are accumulated and tested simultaneously.

Examination of Cerebrospinal Fluid—Lange⁴² describes the performance and interpretation of the various routine tests done on cerebrospinal fluid.

Johnson and Sorum⁴³ observed that the Lange test is read by direct observation in all the laboratories they visited, which necessarily imposes a certain potential source of error, particularly in the hands of the less experienced. Accordingly, they devised a method in which they

41 Mohr, C. F., and Smith, C. A. On the Supposed Daily Variation of the Reagin Content of Syphilitic Serum, *Am J Syph, Gonorr & Ven Dis* **24** 322 (May) 1940.

42 Lange, C. Methods for the Examination of Spinal Fluid, *Am J Syph, Gonorr & Ven Dis* **23** 638 (Sept.) 1939.

43 Johnson, E. R., and Sorum, C. H. The Use of the Photometer in Making Lange Test Readings, *J Lab & Clin Med* **25** 645 (March) 1940.

employed a photoelectric colorimeter and made comparative studies of the results obtained by reading the reaction in the usual fashion and by this means They conclude

The results obtained in these experiments indicate that the photometer provides a very sensitive and accurate method for making Lange test readings However, in practical clinical work, [it] appears to have no advantage over the visual method

Ratio of Blood and Cerebrospinal Fluid Reagin Content—Utilizing a quantitative flocculation technic, Wiener and Derby⁴⁴ compared the reagin titers in a series of 1,245 pairs of specimens of blood and cerebrospinal fluid They found that the amount of reagin in the blood was nearly always more and frequently was a great deal more than the amount present in the corresponding cerebrospinal fluid Thus, they feel, is in support of the theory that reagin present in cerebrospinal fluid is elaborated in the central nervous system

Biologic False Positive Serologic Reactions for Syphilis—Within the past two years, and more particularly during the past year, there has been growing concern over biologic false positive serologic tests for syphilis In discussing this subject an editorial⁴⁵ writer says

Since the introduction of the Wassermann test in 1906, opinion as to the specificity of serologic tests for syphilis, if reports in the literature reflect the general impressions of the times, has passed through three distinct phases From 1906 to 1918, many organic diseases, as well as pregnancy, menstruation, and the effect of various drugs, were reported to cause false positive Wassermann tests In the period 1918 to 1928, these false positive tests were thought to be due to faulty technic or the associated presence of symptomless syphilis, and serologic tests for syphilis were regarded as amazingly specific

From 1928 to the present, the pendulum is again swinging back It now becomes clear that many "false positive" tests are due not to technical but to biologic factors

Two developments have contributed to this reversal of opinion One is the great increase in the number of serologic tests performed Because of laws in many states compelling premarital and prenatal serologic tests for syphilis, and their greatly increased routine use in medical practice, many normal persons or those suffering from infections other than syphilis have been found to give biologic false positive tests

A second and more important factor is the increased sensitivity of modern serologic tests for syphilis In 1918 Mehncke devised a workable flocculation test which was later improved by Kahn, these original tests of Mehncke and Kahn

44 Wiener, A S, and Derby, I M Syphilitic Reagin in Blood and in Spinal Fluid A Comparative Quantitative Study, Arch Dermat & Syph **39** 999 (June) 1939

45 Biologic False Positive Serologic Tests for Syphilis, editorial, Ann Int Med **14** 171 (July) 1940

were less sensitive by 10 to 15 per cent than tests developed after 1928. Hand-in-hand with increased sensitivity came the tendency of these tests to give occasional false positive reactions.

In general, false positive reactions may be of three types. Most frequent are technical false positive reactions due to laboratory errors, which may occur with any type of test. These technical errors are readily recognizable, should cause no confusion in diagnosis and need not be further considered here.

A second category is the biologic false positive tests occasionally encountered in normal persons who have neither syphilis nor any other organic disease. The presence of a reagin-like substance has repeatedly been demonstrated in the serum of many normal animal species other than man. The serum of normal human beings has also been thought to contain a similar reagin-like factor.

The third and last group of false positive serologic tests are those associated with some organic disease other than syphilis, generally an acute infection. The occurrence of these false positive tests in yaws, leprosy, malaria and infectious mononucleosis has been thoroughly established. Other diseases which have been reported to give false positive tests are relapsing fever, rat-bite fever, scarlet fever, tuberculosis, pneumonia, Vincent's infection, malignancy (particularly carcinoma of the tongue), subacute bacterial endocarditis, glanders, Weil's disease, leishmaniasis, lymphopathia venereum, chancroid, trypanosomiasis, typhus fever, vaccinia, upper respiratory infections, rheumatic fever, and injections of horse serum. There are also reports to the effect that certain chemicals, when present in the blood stream, will produce false positive tests, ether anesthesia has been incriminated many times in the older literature, acetic acid poisoning and sulfanilamide have recently been suggested as causing false positive tests.

There is no doubt that some and perhaps many of these diseases will actually cause biologic false positive serologic tests for syphilis. A systematic study with respect to the frequency with which false positive tests do occur is urgently needed. It was not until Ester¹⁶ and Kitchen, Webb and Kupper¹⁶ inoculated nonsyphilitic persons with malaria and tested specimens of blood taken daily from the time of inoculation to several weeks after the temperature became normal that it was realized that not 10 to 15 per cent, as was formerly believed, but a large proportion of the sera (in their series, 90 to 100 per cent) of persons infected with tertian malaria gave biologic false positive tests for syphilis at some time during the course of the infection. A similar approach applied to all the diseases listed above would certainly provide data of clinical significance.

Clarification of the incidence of false positive serologic tests for syphilis in other diseases depends on recognition of the possible transitory nature of biologic false positive tests, and the necessity of repeated tests during the entire course of the disease, continuing well into the convalescent period or until the false reactions have permanently reversed to negative. The application of a quantitative serologic technic to those sera found to be positive should provide data of interest and possible value in the differentiation of biologic false positive tests from those due to actual syphilitic infection.

Clifton and Heinz¹⁶ found that 82 of 5 625 children studied had transient biologic false positive serologic tests for syphilis. Of these, 75 had definite evidence of some type of infection and 61 had fever at the

¹⁶ Clifton, W. M., and Heinz, M. O. A Survey of Prenatal Syphilis in a Hospital for Sick Children. *J. A. M. A.* **114**: 1731 (May 4) 1940.

time blood was drawn for the test which gave a positive reaction. Their findings are tabulated in table 1.

Greval, Sen Gupta and Napier⁴⁷ report a high incidence of biologic false positive Wassermann reactions among patients with kala-azar, and Barnard⁴⁸ describes the case of a patient with a biologic false positive serologic reaction for syphilis caused by vaccinia. The author says that Giordano reported a similar case at the 1938 meeting of the American Society for Clinical Pathology, but search of the indexes discloses no reference to a published report of Giordano's case. In an informal communication, Bay and Sankstone⁴⁹ report that in a large experience with serologic tests in vaccinated persons they have seen no example of a false positive reaction. This experience was confirmed by vaccinating 100 nonsyphilitic patients, 50 male and 50 female, and following the results of the Kahn test at intervals varying between twenty-nine and seventy-

*Patients with One or More False Positive or Doubtful Serodiagnostic Reactions*⁴⁶

Diagnosis	With Fever	Without Fever
Infection of upper respiratory tract uncomplicated	18	8
Infection of upper respiratory tract with complications	22	3
Pulmonary infections (pneumonia, atelectasis, pertussis)	4	2
Local suppuration	4	1
Generalized skin eruptions (eczema, seborrheic dermatitis and dermatitis venenata)	5	3
Pylorospasm	1	
Scurvy	1	
Trauma	3	4
Diagnosis uncertain	3	
Total patients	61	21

six days from the onset of the vaccination "take." In no instance was a positive Kahn reaction encountered. The communication is not sufficiently detailed to constitute conclusive negative information.

Sorba⁵⁰ found that the incidence of syphilis among the 262 patients with carcinoma of the cervix uteri which he studied was 14.1 per cent, whereas it was only 1.6 per cent for the services from which they came and equally low among patients with other types of carcinoma. Impressed by this, he suggests that syphilitic infection must predispose to carcinoma of the cervix. The author does not suggest the alternative

47 Greval, S. D. S., Sen Gupta, P. C., and Napier, L. E. Serologic Reactions in Kala-Azar. Complement-Fixation, False Wassermann Reaction, and High Anti-Complementary Titre, *Indian J. M. Research* **27**: 181 (July) 1939.

48 Barnard, R. D. False Positive Serologic Tests for Syphilis Following Vaccination for Variola, *Illinois M. J.* **77**: 78 (Jan.) 1940.

49 Bay, A. P., and Sankstone, M. I. Effect of Vaccination on Wassermann Tests, *J. A. M. A.* **115**: 475 (Aug. 10) 1940.

50 Sorba, M. Syphilis et cancer du col utérin, *Monatschr. f. Geburtsh. u. Gynak.* **109**: 49 (April), 73 (May) 1939.

explanation that carcinoma in this region may cause false positive serologic reactions for syphilis by becoming secondarily infected with other spirochetes

The occurrence of biologic false positive serologic tests for syphilis in patients with scarlet fever has been a much disputed question. From his experience, Landau⁵¹ concludes that the association must be rare, but from the nature of his observations he can neither disprove the possibility nor arrive at an estimate of the frequency of its occurrence.

To investigate the effect of menstruation in producing false positive reactions, Ingraham and Mayer⁵² did serologic tests for syphilis on sixty-six specimens of blood from 17 healthy young women at varying periods during the menstrual cycle. No positive reactions were obtained either by standard serologic tests or, in 3 additional cases, by a specialized technic calculated to detect subliminal amounts of serum reagin.

With the dawning realization of the frequency and importance of biologic false positive reactions to standard serologic tests for syphilis, Moore⁵³ has briefly outlined certain procedures helpful in establishing this difficult diagnosis, as follows:

(1) Careful history taking as to the symptoms of any acute infection or of serum treatment within a few weeks preceding the questionable serologic test

(2) Careful physical examination for evidence of the above (lymph-nodes, spleen, lungs)

(3) Blood smears for malaria parasites

(4) Blood smears (differential count) for infectious mononucleosis

(5) Blood test for heterophile antibody (infectious mononucleosis)

(6) Repeat serologic tests for syphilis by several different techniques *at least one of which is quantitatively titred*

(a) Suspect as false especially, low titre tests in young persons who, if infected at all, may be presumed to have been recently infected, and if so, should have high titre tests

(b) Suspect as false, also especially, those persons whose tests are paradoxically negative with more sensitive techniques (Kline exclusion, Kahn presumptive, Hinton, Eagle) and positive with less sensitive techniques (Kline or Kahn diagnostic, any complement fixation test)

(7) Repeat test in several different laboratories of known excellence

(a) Suspect as false, tests positive in one laboratory, however excellent, and negative in others

51 Landau, A. Wassermann, Kahn and Sachs-Georgi Reactions in Scarlet Fever, *Acta pædiat* **26** 235, 1939

52 Ingraham, N. R., Jr., and Mayer, V. R. The Menstrual Cycle and the Blood Serologic Test for Syphilis, *Am J Syph, Gonorr & Ven Dis* **24** 23 (Jan) 1940

53 Moore, J. E. A Suggested Method of Approach to the Recognition of the Biologic False Positive Serologic Test for Syphilis, *Bull Genito-Infect Dis* **3** 1 (April) 1940

(8) Test patient's serum by complement fixation with spirochetal antigen (the Reiter strain of *Treponema pallidum*) There is reason to believe that this antigen is much more specific than the beef heart lipid antigens in common use

(9) Test patient's serum with wholly non-specific (e g, bacterial, such as gonococcus, staphylococcus, etc) antigens, and suspect those who react positively with all complement fixation tests

(10) Prolonged serologic follow-up (weeks or months) without antisyphilitic treatment by a good *quantitative* technique, testing blood at frequent intervals Suspect as false positive those sera with markedly fluctuating or spontaneously falling titre

(11) Examine members of family and sexual contacts

(12) Provocative injection of an arsphenamine with following serologic test daily for 14 days by a quantitatively titred technique (the value of this procedure is highly debatable)

(13) Examine the cerebrospinal fluid if a decision cannot be reached earlier

(14) Withhold antisyphilitic treatment until the diagnosis is settled

These procedures are essentially clinical or employ routine serologic tests The serologists, however, also are attempting to devise strictly laboratory methods for the distinction of biologic false positive reactions Kahn ⁵⁴ and Rytz ⁵⁵ describe widely different but equally thaumaturgic methods for the purpose Worthy though these efforts are, they fail entirely to consider the fundamental facts that

(a) Syphilitic reagin has not been identified

(b) Currently employed serologic tests for syphilis (including their own) are entirely nonspecific reactions, since they are based on the use of beef heart antigen

(c) It would seem almost impossible to make a nonspecific reaction specific by a purely manipulative adjustment of that reaction

PUBLIC HEALTH ASPECTS

Syphilis and National Defense—Syphilis has been a major problem both in the army and in the civilian population during every war There were 77,382 recorded instances of the disease in the Union army during the Civil War, and it has been estimated that the United States army lost 2,000,000 man days in the last war because of syphilitic infection It is comforting, therefore, to realize that the potential importance of the problem is not being overlooked in the present national emergency and that in fact it was a matter for consideration some months before the general concern about national defense developed In the course of a

54 Kahn, R L A Serologic Verification Test in the Diagnosis of Latent Syphilis, Arch Dermat & Syph **41** 817 (May) 1940

55 Rytz, F Specificity in the Serodiagnosis of Syphilis A Differential Method, Am J Clin Path **9** 512 (July) 1939

speech in support of an appropriation of \$5,000,000 for the control of venereal disease for the fiscal year of 1939, Congressman Ludlow ⁵⁶ said

One other phase of this problem remains to be discussed. It perhaps is not its most important phase, and yet it is really important. It is the national-defense angle of the problem. There has been much talk of late about where our first line of defense is located. I believe, after all that has been said on the subject, the answer is that our first line of defense is in the fine, healthy, vigorous manhood of America. How can we expect to win wars with men whose morale is broken and whose bodies are weakened by disease? The great justification of this campaign against syphilis is its humanitarianism, but it would also be justified from the standpoint of national defense.

Vonderlehr ⁵⁷ goes into more detail.

There is no better example of the need for intelligent, prolonged national action than the crippling effects of syphilis on our man power.

The United States is planning a concerted drive to bring national defense up to a standard which will insure the future of our government against all conceivable odds. In doing so we must not forget the need for an armed force free from syphilis. We should have learned that lesson well during the World War. Let us review conditions in the male population of military age.

Study of the men drafted in the last war revealed that syphilis was diagnosed by clinical methods alone without the aid of laboratory tests in 19,114 of 2,500,000 men. Only the obvious cases were accounted for since routine serologic tests were not done.

An estimate of the number of men of military age infected with syphilis in the present population has been made from data assembled in recent surveys (1936-1937) in the United States. This study shows that 324,000 of the nation's 20,000,000 men between the ages of 20 and 39 years inclusive would be found so infected. The significance of this estimate is evident when we recall that of our men only 260,783 were killed or injured in action during the entire World War. Thus, casualties due to syphilis at the present time, in this age group, would exceed considerably our total battle casualties during the entire period of the last war.

And this is not the complete story of syphilis as a military problem. An additional 67,000 of the 18,000,000 white men in the age group 20 to 39 years, and an additional 43,000 of the 2,000,000 negro men in the same age group, would acquire syphilis each year. True, prophylactic measures under rigid military control are relatively effective. But the militia must be selected from the civilian man power, and this selection from the total male population available would require several years. With 324,000 syphilitic men at the beginning of hostilities and 100,000 more each additional year, syphilis would indeed become a major problem.

The cost, local, state, and federal, of treating these 324,000 syphilitic men now in peace time would be \$15,000,000 the first year, and each year thereafter the bill would diminish. The Technical Committee on Medical Care stated in its report to the National Health Conference last summer that \$50,000,000 a year

⁵⁶ Ludlow, L. Speech in the House of Representatives, Feb. 24, 1939, reprinted, *J. Social Hyg.* **25** 275 (June) 1939.

⁵⁷ Vonderlehr, R. A. Recent Progress Against Syphilis and Gonorrhea and Its Relation to the National Defense, *Am. J. Syph., Gonorr. & Ven. Dis.* **23** 506 (July) 1939.

would be necessary to bring syphilis and gonorrhea under control in the entire population. In this connection, the people of the country have some pertinent decisions to make about the public health.

We as a nation have agreed that we must have a strong national defense. We have unhesitatingly authorized the purchase of flying fortresses at a cost of \$285,000 each and the construction of battleships at a cost of \$70,000,000 each.

Armaments are essential to national defense. Alone they do not prepare us for war. Much depends upon the physical fitness of the men who man them.

Is it not a waste of money and of men to spend millions on the treatment of syphilitic soldiers as we did during and shortly after the World War and to provide inadequately for the civilian control of syphilis beforehand?

Should not adequate provisions be made for civilian syphilis control not alone for humanitarian reasons, but as an essential in the national defense program?

The public health stage is set. A successful war against syphilis is assured. Now is the time to act.

Lorenz and Bleckwenn⁵⁸ estimate that the number of enlistments from the state of Wisconsin in World War I was 140,000 and that routine serologic tests for syphilis could have been done on the entire number for \$1,200. There have been 129 patients with neurosyphilis cared for by the Veterans' Bureau from this group, and it has been estimated that the cost of caring for all ex-service men who have become disabled because of syphilis exceeds \$100,000,000. Because syphilis exerts such a tremendous tax, not only during the military period but during the postwar period, the authors urge more attention to its discovery and control in a future mobilization.

Heagerty⁵⁹ reviews the experience of the Canadians in World War I and for the present emergency suggests the establishment of a military department of venereal disease control to deal with the question of prevention and treatment of syphilis in soldiers, closely coordinated with a civilian committee of venereal disease control to handle the problem among the civilian population.

The London correspondent for *The Journal of the American Medical Association* writes⁶⁰

In the four years of the World War 400,000 cases of venereal disease occurred in the British army, representing a great loss of fighting power. The practice when a soldier was infected was to evacuate him from his unit to a hospital for venereal disease at the base, where he remained until cured or judged to be non-infectious. In some cases men on home leave deliberately acquired venereal disease, usually gonorrhea, in order to avoid returning to the front line. In large towns prostitutes suffering from venereal disease specialized in accosting soldiers and telling them that intercourse would enable them to acquire the disease with the

58 Lorenz, W. F., and Bleckwenn, W. J. Syphilis and Mobilization, *Mil Surgeon* **85** 197 (Sept.) 1939.

59 Heagerty, J. J. Venereal Disease Control During Wartime, *Canad. Pub. Health J.* **30** 567 (Dec.) 1939.

60 Control of Venereal Disease in the War, *Foreign Letters*, *J. A. M. A.* **114** 266 (Jan. 20) 1940.

advantage of being sent to the base. There were instances of men inoculating the urethra with pus obtained from a friend suffering from gonorrhea. In the present war the military authorities have adopted a different system. Except in cases presenting serious complications all men in the early stages of syphilis, or suffering from acute anterior gonorrhea or soft sore, will be treated in the field and not evacuated to a special hospital at the base. The advances in the therapy of venereal diseases made since the last war enable treatment in the field to be more readily carried out. A venereologist of wide experience, Col B L Ank, has been lent to the army by the Ministry of Hygiene to direct the venereal diseases branch. At the base is a large hospital for venereal diseases where complicated cases, including those of untoward effects of therapy, are treated.

Control of Venereal Disease in the United States—Snow⁶¹ provides a summary of the important features and mode of operation of the federal act to control venereal diseases, which is detailed elsewhere⁶²

An Act to Impose Additional Duties upon the United States Public Health Service in Connection with the Investigation and Control of the Venereal Diseases, Public Law 540, 75th Congress of the United States, Approved, May 24, 1938

AN ACT—"To impose additional duties upon the United States Public Health Service in connection with the investigation and control of the venereal diseases"

SEC 4a For the purpose of assisting States, counties, health districts, and other political subdivisions of the States in establishing and maintaining adequate measure for the prevention, treatment, and control of the venereal diseases, for the purpose of making studies, investigations, and demonstrations to develop more effective measure of prevention, treatment, control of the venereal diseases including the training of personnel, for the pay, allowances and traveling expenses of commissioned officers and other personnel assigned to duties in carrying out the purposes of sections 4a to 4c, inclusive, of this Act in the District of Columbia and elsewhere, and for the printing of reports, documents, and other material relating thereto, there is hereby authorized to be appropriated for the fiscal year ending June 30, 1939, not exceeding the sum of \$3,000,000, for the fiscal year ending June 30, 1940, not exceeding the sum of \$5,000,000, for the fiscal year ending June 30, 1941, not exceeding the sum of \$7,000,000, and for each fiscal year thereafter such sum as may be deemed necessary to carry out the purposes of sections 4a to 4e, inclusive, of this Act

SEC 4b Prior to the beginning of each fiscal year the Surgeon General of the Public Health Service shall determine, out of the appropriations made pursuant to *Section 4a*, the sum to be allotted to the several States, including the District of Columbia, Alaska, Puerto Rico, Virgin Islands and Hawaii. The Surgeon General shall then allot such sum to the several States upon the basis of (1) the population, (2) the extent of the venereal-disease problem, and (3) the financial needs of the respective States. Upon making such allotments he shall certify the amounts thereof to the Secretary of the Treasury. The amount of an allotment to any State for any fiscal year remaining unpaid at the end of such

61 Snow, W F. Syphilis and Federal Assistance in the States to Date, J Social Hyg 25 271 (June) 1939

62 Control of Venereal Disease in the United States. Present and Future Plans, Ven Dis Inform, 1940, supp 10

fiscal year shall be available for allotment to the States for the succeeding fiscal year in addition to the amount appropriated and available for such fiscal year

SEC 4c Prior to the beginning of each quarter of the fiscal year the Surgeon General of the Public Health Service shall determine the amount to be paid to each State for such quarter from the allotment to such State, and shall certify the amount so determined to the Secretary of the Treasury Upon receipt of such certification, the Secretary of the Treasury shall, through the Division of Disbursement of the Treasury Department and prior to audit or settlement by the General Accounting Office, pay in accordance with such certification The moneys so paid to any State shall be expended in carrying out the purposes specified in section 4a, and in accordance with plans presented by the health authority of such State and approved by the Surgeon General of the Public Health Service

SEC 4e With the approval of the Secretary of the Treasury and after consultation with a conference of State and Territorial health officers, the Surgeon General of the Public Health Service is authorized to prescribe the rules and regulations necessary to carry out the purposes of Sections 4a to 4e, inclusive, of this Act

Control of Syphilis in the South—Burney⁶³ discusses the advantages of the mobile clinic (a specially built trailer or light truck equipped for routine diagnostic and treatment methods) in the control of syphilis in rural districts in the South Such a unit has been in operation in the remote counties of the Georgia coast,⁶⁴ which consist mostly of pine woods and swamp and are inhabited by Negroes employed in the essentially decentralized turpentine, lumber and fishing industries The incidence of syphilis among these people has been estimated to be 27 per cent This author expresses the belief that in such a district the mobile unit has many advantages over a stationary clinic It covers a large territory in a short time, it can be operated easily and quickly, it is interesting to the patients, it is good advertisement for the health program, and, finally, it is economical

A similar unit is in operation in Alabama⁶⁵

Control of Syphilis in Memphis—In developing a program for the control of syphilis in Memphis and Shelby County, Tenn, McGinnes and Packer⁶⁶ felt that a widespread blood-testing campaign which would uncover thousands of previously untreated patients with positive serologic reactions would be unwise, because it would represent dissipation of efforts away from the fundamental public health problem involved They determined, therefore, to conserve effort and direct it toward an attempt

63 Burney, L E Control of Syphilis in a Southern Rural Area A Preliminary Report, *Am J Pub Health* **29** 1006 (Sept) 1939

64 Davenport, W Bad Blood Wagon, *Collier's* **103** 9 (May 27) 1939

65 A New Traveling Unit of the Treatment of Syphilis, *J M A Alabama* **9** 193 (Dec) 1939

66 McGinnes, G F, and Packer, H A Program for the Control of Syphilis, *South M J* **33** 78 (Jan) 1940

to control communicable syphilis. To accomplish this they developed an active follow-up system to keep patients with potentially infectious syphilis under treatment until they had received at least twenty injections of an arsphenamine and an equivalent amount of heavy metal, epidemiologic investigation was given a large part in the program.

Adequate treatment was provided for by the establishment of the necessary clinic facilities and the encouragement of cooperation from the private practitioners, to whom in turn the public health officials offered follow-up services and epidemiologic investigations and free laboratory and consultation service with free drugs for the treatment of all patients reported to the health department.

Public Interest in Venereal Disease—A commentator⁶⁷ says that in the past fiscal year there were 2,405 clinics in the United States which were treating syphilis, an increase of 287 per cent over the fiscal year of 1930. Also in the past fiscal year 10,656,253 doses of an arsenical drug were used in the treatment of syphilis, an increase of 84 per cent over 1933. There were more than 5,000,000 blood tests made in the United States during the past fiscal year, whereas in 1930 only 1,632,082 blood tests were reported. The writer expresses the belief that these marked increases reflect the greater public interest in venereal disease control.

Syphilis Among Criminals—At the time of writing, the Woodbourne Institution for Defective Delinquents occupies a unique position among the correctional institutions of the state of New York, in that it houses both mentally defective and normal prisoners. Their criminal, social and mental histories range in extremes. From an analysis of the records of the prisoners admitted during a period of sixteen months ending in May 1939, Rubin⁶⁸ concludes as follows:

This survey discloses the prevalence of syphilis in 13.9% of the prisoners, in a total population of 718 men. The white syphilitics constitute 57.1% of the total population, 7.36% of their own racial group and account for 42.71% of all syphilitics. The colored syphilitics constitute 7.52% of the total population, 33.75% of their own racial group and account for 56.25% of all syphilitics. Also noteworthy is the fact that 83.3% of the native-born colored syphilitics are from the southern states.

Asymptomatic syphilis is more common than is generally supposed, 68.7% of all syphilitics were unaware of their infection prior to their admission to a correctional institution.

The greatest incidence of syphilis is found among men of low intelligence, single men, and in the chronological age group of 25 to 44 years. The men with Mental Ages of 6 to 9 years and Intelligence Quotients of 40 to 60, constitute

67 Public Interest in Venereal Disease, Current Comment, J. A. M. A. **113**: 2422 (Dec. 30) 1939.

68 Rubin, J. Syphilis Among Criminals, J. Crim. Psychopath. **1**: 112 (Oct.) 1939.

78.0% of all syphilitics, the single men constitute 74.9% of all syphilitics, and the men in the chronological age groups of 25 to 44 years constitute 65.6% of all syphilitics

Twenty-six inmates, 27% of all syphilitics, submitted to spinal punctures, disclosing three cases of asymptomatic neurosyphilis. Therefore, as an aid to diagnosis and treatment, measures should be instituted to make such tests compulsory for all syphilitics, and as often as necessary at the discretion of the physician

Syphilis and Industry—With the increasing use of routine pre-employment serologic tests for syphilis and the growing acceptance of the proper concern of the employer with the health of his employee, attention is being turned to the development of syphilis control programs in industrial organizations. At present only a small beginning has been made, and as yet there is no unanimity of opinion on several important questions. No recorded effort has been made to reconcile the rights, privileges and responsibilities of the employee, the employer and the public welfare. This is well illustrated by the variant opinions expressed by the leaders of thought on the subject who participated in a symposium under the auspices of the Annual Congress on Industrial Health.⁶⁹

Best thought at the moment, however, is summarized in the recommendations of the Surgeon General of the United States Public Health Service, as related by Russell.⁷⁰

- 1 Routine blood tests should be made on all employees at times of reexamination
- 2 Routine blood tests should be made on all applicants for employment
- 3 Patients with syphilis, if noninfectious, should be kept in employment and also accepted for work provided they agree to take the necessary treatment for syphilis. Those refusing treatment must be referred to the local health departments
- 4 All persons with syphilis found by blood testing should be referred to the family physician for confirmation of the diagnosis and for treatment of the disease. If the worker is unable to pay for this service, he should be referred to clinics where diagnosis and treatment are available
- 5 Strict confidence must be maintained between the plant physician and the worker regarding his condition
- 6 Cases should be followed up by the plant physician and his staff to assure that the patient continues treatment and that adequate treatment is being received. If facilities are available, health departments may assist in the follow-up of cases
- 7 An educational program should be developed which will teach the employees the facts about venereal diseases, how they are contracted, how they are spread and how they may be cured. The educational program should include information concerning prophylaxis

Even here paragraph 3 clearly by implication advises that treatment be made compulsory (i.e., under threat of discharge or refusal of

⁶⁹ Syphilis and Employment, Official Notes, J. A. M. A. **114** 895 (March 9) 1940

⁷⁰ Russell, A. E. Syphilis Case Finding in Industry, J. A. M. A. **114** 1321 (April 6) 1940

employment) for patients who are not infectious. The advisability of treatment for such patients is not called into question, but the fundamental concept of this type of compulsion so clearly violates the right of free choice of the individual person as, in our opinion, to render it highly undesirable. Would it not be better to make only the requirement that the patient consult his physician or a medical agency? In the long run this probably would accomplish as much effective treatment for the cooperative patients and no less treatment for the uncooperative and would avoid entirely a potentially objectionable situation.

Butt⁷¹ places his finger on one of the difficulties in developing a syphilis control program in industry by calling attention to the fact that in many industrial hospitals a patient may receive proper diagnosis and capable treatment for a broken leg, typhoid fever or tuberculosis, but not always for syphilis. A plan for the diagnosis, follow-up and treatment of railroad employees with syphilis is suggested.

Wilzbach⁷² describes the development of interest in the syphilis control plan in Cincinnati and preliminary results to date.

The Teaching of Syphilis—Nelson⁷³ is encouraged by the trend of medical schools toward the teaching of syphilis in the department of internal medicine. The emphasis is now being placed on the fact that syphilis is a communicable, systemic disease, which is only incidentally dermatologic. He interprets the present trend to indicate that the medical profession is becoming interested in the better treatment of this disease by every physician.

DRUGS

Spirocheticidal Activity of Arsenicals in Vitro and in Vivo—Following the demonstration by Eagle¹⁶ of the spirocheticidal activity in vitro of arsenical compounds used in the treatment of syphilis, Kolmer, Kast and Rule⁷⁴ sought to determine whether the therapeutic effectiveness of a drug could be so assayed. They report that the spirocheticidal activity in vitro of arsphenamine, neoarsphenamine and other arsenical compounds cannot be used as a measure of their curative value. It should be emphasized, however, that the results detailed in the following quotation from Kolmer and his associates cannot be accepted as contradiction of Eagle's

71 Butt, E. M. Syphilis in Railroad Medicine. A General Consideration of the Problem, *Indust Med* 8:465 (Nov.) 1939.

72 Wilzbach, C. A. A Syphilis Control Program in Industry, *J. Social Hyg* 26:49 (Feb.) 1940.

73 Nelson, N. A. The Place of Syphilis and Gonorrhea in Medicine, *Bull. Genito-Infect. Dis.* 9:1 (Dec.) 1939.

74 Kolmer, J. A., Kast, C. C., and Rule, A. M. The Spirocheticidal, Trypanocidal and Mechanism of Activity of Organic Arsenical Compounds in Vitro and in Vivo in Relation to Therapeutic Effectiveness, *Am. J. Syph., Gonorr. & Ven. Dis.* 24:201 (March) 1940.

work, because of essential differences in the technical methods employed in the two studies

1 Variable factors referable to serum, tissue extractives, temperature, and time of exposure and number of spirochetes exposed to the immobilizing and spirocheticidal effects of arsenical compounds in vitro, render these tests unsuitable as a measure of therapeutic effectiveness

2 The approximate highest final dilutions of one lot of arsphenamine and nine lots of neoarsphenamine producing marked immobilization of virulent *S pallida* from rabbit testicular syphilomas in an exposure of fifteen minutes at room temperature (24 to 27°C), varied for arsphenamine from 1 1,000 to 1 20,000, with the majority of the lots of neoarsphenamine varying from 1 5,000 to 1 10,000. In terms of arsenic the immobilizing dilutions of arsphenamine and neoarsphenamine varied from 1 5,000 to 1 100,000

3 The approximate minimal curative doses required for the biologic cure of rabbits with acute testicular syphilis were 0.012 Gm of arsphenamine and 0.020 Gm of neoarsphenamine per kilogram of weight

4 One lot of sulpharsphenamine immobilized at 1 1,000 (1 5,300 arsenic) with a curative dose of 0.020 Gm per kilogram, one lot of mapharsen immobilized at 1 1,000 (1 3,500 arsenic) with a curative dose of 0.005 Gm per kilogram, one lot of tryparsamide immobilized at 1 1,000 (1 4,000 arsenic) with a curative dose of 0.8 Gm per kilogram, and one lot of bismarsen immobilized at 1 500 (1 3,850 arsenic) with a curative dose of 0.015 Gm per kilogram

5 Immobilization of *S pallida* in cultures in a medium carrying 10 per cent serum was very much less. The lot of arsphenamine gave marked immobilization at 1 640, five of the lots of neoarsphenamine varied from 1 20 to 1 40, the one lot of sulpharsphenamine immobilized at 1 40, the one of mapharsen at 1 160, the one of tryparsamide at 1 20, and the one of bismarsen failed at 1 20

6 The same variable factors referable to serum, time and temperature of exposure, and number of parasites exposed apparently influence the effects of arsenical compounds upon the immobilization of *T equiperdum* in vitro, although not to the same extent as in tests employing *S pallida* because of the greater technical ease in controlling them

11 With arsphenamine and neoarsphenamine the immobilization of *T equiperdum* in vitro is in sufficiently close relationship to curative activity in vivo to be of probable value as a measure of therapeutic effectiveness

12 The minimal curative dose of arsphenamine in rabbit syphilis (about 0.012 Gm per kilogram) is about two to three times higher than the minimal curative dose in trypanosomiasis by the Kolmer method (0.004 to 0.008 Gm per kilogram). The minimal curative dose of neoarsphenamine in rabbit syphilis (0.020 Gm per kilogram) is about three times higher than the minimal curative dose in trypanosomiasis (0.006 to 0.008 Gm per kilogram). The minimal curative dose of sulpharsphenamine by intravenous injection in rabbit syphilis (0.020 to 0.022 Gm per kilogram) is about two times higher than the minimal curative dose in trypanosomiasis (0.012 Gm per kilogram). The minimal curative dose of mapharsen in rabbit syphilis (0.005 Gm per kilogram) is about two to three times higher than the minimal curative dose in trypanosomiasis (0.002 Gm per kilogram). The minimal curative dose of tryparsamide in rabbit syphilis (0.800 Gm per kilogram) is about four times higher than the minimal curative dose in trypano-

somiasis (0.200 Gm per kilogram) The minimal curative dose of bismarsen by intramuscular injection in rabbit syphilis (0.015 Gm per kilogram) is about the same as the minimal curative dose in trypanosomiasis It therefore appears that the determination of the minimal curative doses of these arsenical compounds in the treatment of *T. equiperdum* infections of rats may be acceptable as a measure of spirocheticidal activity, and may be preferable to the determination of immobilization of *S. pallida* or *T. equiperdum* in vitro for this purpose

Arsphenamine—Cannon⁷⁵ believes with many that old arsphenamine is the drug of choice but feels that it is not used often enough because of the technical difficulties involved in its administration To obviate these he has developed a technic whereby it may be administered by syringe He reports the results of the administration of 16,943 injections of old arsphenamine to 1,053 adults and 134 children by this method The drug was diluted in 10 cc per decigram for adults and 5 cc per decigram for children The average dose for men was 0.2 to 0.4 Gm and for women 0.15 to 0.30 Gm Approximately 77 per cent of the adult patients tolerated the concentrated injections well There were no unusual reactions, the proportion of severe delayed reactions was smaller but there were more immediate mild reactions, most of which were of the nitritoid type

Neoarsphenamine—Disturbed by the lack of agreement among previous observers concerning the minimal curative dose of neoarsphenamine for rabbit syphilis, Probey⁷⁶ presents as another of the growing list of contributions on the pharmacology of the drug from the National Institute of Health a detailed consideration of the spirocheticidal activity of the seven American brands in experimental syphilis in the rabbit Feeling that the differences recorded by various observers might largely be due to variations in experimental technic, this worker carefully standardized experimental procedures In addition, a "control brand" of neoarsphenamine was included in each series of observations He found the minimal effective dose to vary from series to series and emphasized that each test must be considered independently and comparisons made only with the control product for that series When this was done, no significant differences were noted in the sterilizing power of the seventeen lots (representing seven brands) of neoarsphenamine which were studied From the composite protocol the minimal effective dose could be placed at 40 mg per kilogram, since this cured 94 per cent of 54 rabbits

75 Cannon, A. B. A Simplified Technique for Administering Old Arsphenamine. A Report on 16,943 Injections Given at the Vanderbilt Clinic, *Am J Syph, Gonorr & Ven Dis* **23** 621 (Sept.) 1939

76 Probey, T. F. The Relation Between the Trypanocidal and Spirocheticidal Activities of Neoarsphenamine. V. The Spirocheticidal Activity of the Several American Brands of Neoarsphenamine, *Pub Health Rep* **54** 2242 (Dec. 22) 1939

Solusalvarsan—Solusalvarsan is the European trade name for a 7 or 10 per cent glycerol solution of 3,4 diacetylamino-4-oxyarsenobenzene-2 glycolate. The compound itself contains about 20 per cent of trivalent arsenic, and the prepared solution is locally well tolerated following intramuscular injection in amounts equivalent in arsenic content to the usual doses of the compounds which must be given intravenously. It has enjoyed desultory use in European clinics for several years, but the published reports concerning it have reflected so poor critique that aside from one¹⁶ they have been omitted from the previous reviews. There is now available a critical report by Harrison⁷⁷ on results from its use in England, and currently the drug has been subjected to searching experimental and clinical trial in the United States. The results of this trial are as yet unpublished, but it is fair to say that the American experience has been no more happy than the English.

On behalf of the Therapeutic Trials Committee of the British Medical Research Council, Harrison reports his analysis of the results from the use of solusalvarsan in selected clinics of the Ministry of Health. He says

All the observers who collaborated in this investigation agreed in finding that the therapeutic power of Solu-salvarsan, weight for weight, was quite distinctly less than that of neoarsphenamine. This was shown in the persistence of *S. pallida* in chancre juice after administration of the remedy and in the slower healing of lesions.

Toxic reactions were unduly frequent. The number of cases treated with two or more doses of Solu-salvarsan by six observers, whose results are described above, was 42, and dermatitis was recorded in 12, jaundice in 3 and herpes of the face in 1, also severe pain at the site of injection was reported in 3 cases. The details do not support any suggestion that the toxic effects were due to excessive dosage, as the dermatitis occurred after less than five injections in 8 of the dermatitis cases, and all those in which jaundice occurred, as also the herpetic eruption of the face, followed the second injection.

Tryparsamide—In a review of the literature which is so compact that further condensation is impossible Hinrichsen⁷⁸ refers to one hundred and seventy-five well chosen articles dealing with the pharmacology, toxicology and effect of tryparsamide on the optic nerve and the use of the drug in the treatment of syphilis.

Induced Tolerance to Arsenic—Kuhls, Longley and Tatum⁷⁹ report the development of tolerance to several organic compounds of arsenic by

77 Harrison, L. W. Solu-Salvarsan. Toxicological and Therapeutic Tests Made on Behalf of the Therapeutic Trials Committee of the Medical Research Council, Brit J Ven Dis 15 203 (July) 1939.

78 Hinrichsen, J. Tryparsamide in the Treatment of Syphilis. Review of Literature, Ven Dis Inform 20 293 (Oct) 1939.

79 Kuhls, M. L., Longley, B. J., and Tatum, A. L. Development of Tolerance to Organic Arsenicals in Laboratory Animals, J Pharmacol & Exper Therap 66 312 (July) 1939.

laboratory animals They found experimentally (usually in rats) that tolerance did not develop unless the initial dose was over 50 per cent of the single tolerated dose and that there was an optimum time interval between injections Some compounds studied could be made to produce no increase in tolerance, those which did were grouped as producing a 100 to 200 per cent or a 50 to 90 per cent increase, respectively There was no correlation between molecular figures or composition and the phenomenon, but it could not be developed to inorganic arsenical compounds, neoarsphenamine or sodium cacodylate

Finally, of great interest is their discovery that if animals tolerant to trypanisamide were infected with *Trypanosoma equiperdum* they still could be cured with the minimal curative dose of the drug, which has the obvious effect of increasing its therapeutic index

Sobisminol—The report of the Council on Pharmacy and Chemistry of the American Medical Association⁸⁰ admirably summarizes the experimental and clinical evidence regarding the usefulness of sobisminol, including the papers of Meininger and Barnett⁸¹ and Scholtz, McEachern and Wood⁸² which appeared simultaneously The report says

In view of the evidence, it would appear that sobisminol solution administered by the *intramuscular route*⁸³ (*a*) exerts a definite antisymphilitic effect in experimental syphilis in the rabbit in doses of about 5 mg per kilogram of body weight, (*b*) exerts a definite curative effect in experimental syphilis in the rabbit in a minimum curative dose of about 7 mg per kilogram of body weight, (*c*) causes the disappearance of *Spirochaeta pallida* from chancres and condylomas of human beings in a period of from four to seven days, (*d*) acts to clear primary syphiloderms in about ten days, secondary syphilitic lesions in an average of about fourteen days, and tertiary syphilitic lesions in about thirty days, (*e*) acts satisfactorily in causing the reversal of the positive serologic blood reaction, (*f*) is moderately well tolerated after local injection, (*g*) produces a urinary excretion of bismuth as high as or higher than any other bismuth compound now employed in the treatment of syphilis, and (*h*) is followed by no greater incidence of relapse than after administration of other bismuth compounds From the foregoing it is apparent that sobisminol solution offers a means of obtaining, by *injection treatment*,⁸³ the systemic effects of bismuth in the treatment of syphilis

In evaluating a bismuth compound which is to be administered *orally*,⁸³ there are certain disadvantages which must be considered Thus, with sobisminol mass a large number of the patients have gastrointestinal upsets, occasionally severe enough to cause discontinuance of the drug, bismuth stomatitis is seen occasionally, a bismuth line is not rare There appears to be a tendency for some individuals to neglect their treatment as soon as they begin to feel better Some of the patients

80 Sobisminol Mass and Sobisminol Solution, Report of the Council on Pharmacy and Chemistry, J A M A **113** 2235 (Dec 16) 1939

81 Meininger, W M, and Barnett, C W The Treatment of Syphilis with Sobisminol Mass Given by Mouth, J A M A **113** 2214 (Dec 16) 1939

82 Scholtz, J R, McEachern, K D, and Wood, C Sobisminol Mass Clinical Results with Oral Administration, J A M A **113** 2219 (Dec 16) 1939

83 The italics are ours

examined by Meininger and Barnett were found to have no bismuth in the urine, but it is believed that they were patients who had neglected the treatment. When injections are being given at stated intervals, the patient arranges for this treatment, knows when he is due for it and usually appears. On the other hand, if he is simply given some capsules to take, he may forget to take them or he may leave them at home and in that way be negligent in their use. Moreover, because of gastrointestinal intolerance the patient may become discouraged in the early stages of his syphilis at a time when treatment is most necessary. These factors acquire greater significance when it is considered that no sustained bismuth effect is derived from the use of sobisminol capsules, judging by the rapid drop of urinary bismuth excretion as soon as the capsules are stopped. It is not surprising, therefore, that Scholtz, McEachern and Wood noted two cases of relapse in early syphilis within two weeks after sobisminol capsules were stopped. Meininger and Barnett also speak of this danger.

The relapse tendency when oral bismuth as a medication is employed is unfortunate, because it is in the first stages of syphilis that the relapses are most frequently seen. If a bismuth preparation is employed which allows the anti-syphilitic effect to cease soon after its administration is stopped, with no bismuth depots in the body, there is more danger of relapse than when continuous bismuth injections are carried out.

Finally, there is danger of self medication from the use of sobisminol mass. In such case an individual, unaware of the true character of the syphilis, may use sobisminol mass for a time, perhaps not in the proper dose, until he feels better, and then stop further treatment. As a result, an early infectious relapse and the consequent spread of the disease to other persons might occur.

It must be noted that the administration of sobisminol mass in capsules by the oral route (a) results in an effect comparable to sobisminol injection therapy in sterilizing syphilis in rabbits and in destroying organisms in local chancres, (b) produces rapidly, in a dose of three capsules three times a day, a high urinary bismuth excretion, comparable to that of any other bismuth compound studied thus far, (c) causes primary syphiloderms to clear in about ten days, secondary lesions in about fourteen days and tertiary lesions in about thirty days, (d) results in satisfactory action in reversing positive serologic tests, and (e) exerts a definite action in the treatment of syphilis, clearing chancres and condylomas.

There is a definite place for oral therapy with sobisminol mass in the treatment of syphilis, although probably not so much in the early stages as in the latent period or in the later stages of the disease. It should be useful in certain early cases of syphilis to provide continuity when conditions necessitate the patient's being absent from the physician for a matter of a week or more. It is suggested, however, that intramuscular therapy is preferable in all early syphilis, if it is possible, for the purpose of maintaining continuous therapy, if for no other reason. Attention is directed to the fact that no bismuth depot is established when the product is administered solely by the oral route. From the experimental and clinical evidence described, it must be noted that the last course of bismuth therapy should be given as a series of insoluble injections, in order to establish bismuth depots for continuation of sustained bismuth effects.

Bismuth in Tissues—At postmortem examination Scholtz and Chaney⁸⁴ determined the bismuth concentration in the tissues of 15 patients who had been treated with the drug.

84 Scholtz, J. R., and Chaney, A. L. Studies in the Tissue Concentration of Bismuth in Man, *Am J Syph, Gonorr & Ven Dis* 23:759 (Nov) 1939.

In the kidney we found bismuth concentrations ranging from 0.5 to 120 mg per 100 gm of tissue, and in the liver from 0.5 to 45 mg per 100 gm of tissue.

In several instances large amounts of bismuth are present even though several years have elapsed since the last injection was administered. The concentration in the kidney is consistently higher than in any other tissue examined, and this preponderance seems to increase as time elapses.

Although we have not attempted a correlation of tissue concentration of bismuth with the histologic findings, it should be stated that in several instances the concentration was greater in cases in which no tissue change was present than in several in which definite lesions present were probably attributable to the bismuth. It is therefore suggested that bismuth concentration per se is not the only factor of importance in the production of actual tissue damage, and that other factors, such as time during which bismuth is deposited, may greatly influence the effects which a given amount of the drug may produce.

Bismuth and Lead—Epstein⁸⁵ brings out that in comparison with the other drugs employed in the treatment of syphilis, the bismuth preparations show a notably low toxicity. On the other hand, abdominal cramps, diarrhea, polyneuritis, psychic symptoms and erythropoietic disturbances have been reported following their administration. He suggests that some of these reactions may actually have been the result of lead poisoning and not of bismuth intoxication at all.

In support of this contention he presents the cases of 2 patients, a painter and a smelter, both of whom had been chronically exposed to lead for long periods. In these patients signs and symptoms of lead poisoning followed the administration of bismuth, subsided with the passage of time and did not recur on subsequent treatment with bismuth. As to the mechanism by which this occurred, the author suggests that bismuth may replace lead stored in the bones and promote its mobilization with the development of acute symptoms in a person who is chronically absorbing and storing amounts of lead small enough not to produce clinical symptoms.

Local Tolerance of Injected Bismuth—On the basis of the administration of seven hundred and twenty injections of a standard suspension of bismuth subsalicylate in oil to which 3 per cent chlorobutanol had been added, controlled by the administration of an equal number of injections of the oil suspension alone, Hoefer⁸⁶ found that the addition of chlorobutanol did not reduce or increase local reactions or symptoms attributable to the injection.

Other Drugs—Doak, Eagle and Steinman⁸⁷ have prepared a series of monosubstituted phenylarsenoxides with a view of studying their

85 Epstein, E. Effects of Bismuth Therapy on Latent Plumbism. Preliminary Report, Arch Dermat & Syph **41** 38 (Jan) 1940.

86 Hoefer, H. F. Effect of Adding Chlorobutanol to Bismuth Subsalsalicylate in Oil Injected Intramuscularly, Arch Dermat & Syph **41**:380 (Feb) 1940.

87 Doak, G. O., Eagle, H., and Steinman, G. H. The Preparation of Phenylarsenoxides in Relation to a Projected Study of Their Chemotherapeutic Activity. I. Monosubstituted Derivatives, J Am Chem Soc **62** 168 1940.

action against *S. pallida*. They describe five new arsenoxide compounds and provide additional data on some of those already known. The present paper is preliminary. Pereira⁸⁸ finds that vanadium sodium tartrate is an effective antisyphilitic drug. Pariser⁸⁹ gave sulfanilamide to 18 patients with late latent syphilis. No influence on the reversal of the serologic tests for syphilis was observed.

Sodium Thiosulfate—From a review of the literature relative to the clinical and experimental evidence for the value and action of sodium thiosulfate, sodium formaldehyde sulfoxylate and other sulfur-bearing compounds in poisoning by various metallic salts, particularly arsenic and mercury, Muir and her collaborators⁹⁰ bring out that there has been a great deal of contradictory evidence. Work with experimental animals tends to indicate, however, that none of these compounds is useful in protecting against poisoning with arsenic or mercury unless perhaps if given in such a highly specialized way (for example, prior to the administration of the poisoning compound) as to have no promise for clinical application. Their own studies carried out on 123 rabbits poisoned with inorganic and organic arsenic and mercury compounds failed to show any protective action of sodium thiosulfate or of sodium p-sulfhydryl-phenylsulfonate as used in various ways. Histologic examination of the kidneys of animals poisoned by sodium arsenite showed the same degree of degeneration regardless of which presumably protective drug had been administered.

In spite of this, the laboratory workers, apparently under pressure from the clinicians, attempt to raise the argument that some of the clinical reports are so emphatic in claims for benefit from the use of sodium thiosulfate and less commonly from the other compounds in the treatment of arsenical reactions in human beings that these drugs must be responsible. They feebly conclude, therefore, that further study is necessary.

Vaccine—Bruder⁹¹ briefly reviews the literature on the attempts which have been made to develop a vaccine for the prevention and treat-

88 Pereira, J. Das Vanadium bei der Behandlung der menschlichen Protozoenerkrankungen, *Ztschr. f. Immunitätsforsch. u. exper. Therap.* **97**: 77 (Nov. 17) 1939.

89 Pariser, H. The Use of Prontylin in Seroresistant Syphilis, *Am. J. Syph., Gonorr. & Ven. Dis.* **24**: 48 (Jan.) 1940.

90 Muir, K. B., Stenhouse, E., and Becker, S. W. Action of Sulfur-Containing Compounds in Arsenical and Mercurial Poisoning with Review of the Use of Sodium Thiosulfate in Dermatologic Practice and Report of Experiments on Rabbits with Sodium Thiosulfate, Sodium P-Sulfhydryl Phenyl Sulfonate and Sodium Formaldehyde Sulfoxylate, *Arch. Dermat. & Syph.* **41**: 308 (Feb.) 1940.

91 Bruder, K. Unsere Erfahrungen mit Spirochatenvakzine (Hilgermann), *Dermat. Wchnschr.* **110**: 173 (March 2) 1940.

ment of syphilis and makes the obvious point that most such efforts have died aborning because of failures to cultivate virulent *S. pallida* on artificial culture mediums. In 1931, however, Hilgermann succeeded in isolating an organism, morphologically typical of *S. pallida* but non-pathogenic for experimental animals, which he could grow in massive cultures and from which he prepared a vaccine. In the present communication, Bruder reports the use of this material in the treatment of 95 patients with various forms of syphilis. The technic of treatment was to inject 0.25 to 1.0 cc of the vaccine subcutaneously for a total of ten injections in eight days. The author reports that of the 95 patients so treated 61 (64.2 per cent) were improved. Unfortunately, however, he places no emphasis on the fact that all or most of the patients had treatment by the more usual methods in addition to the vaccine therapy, that is, patients with early syphilis received neoarsphenamine and those with neurosyphilis inoculation malaria, etc. Under these circumstances, it is obviously impossible to pass any judgment on the value of the vaccine treatment.

In the brief consideration given to the use of vaccine in diagnosis, Bruder observes that the local reaction to the injection of spirochete vaccine is not entirely specific and therefore must be interpreted with care.

UNTOWARD EFFECTS OF TREATMENT

Arsenical Dermatitis—Stephenson and Chambers⁹² report the incidence of arsenical dermatitis observed in 1938 by naval medical officers. During this year there were 123,176 doses of arsenicals administered. Forty patients sustained reactions, and of these 25, or 62.5 per cent, had dermatitis in some form.

In these 25 cases of dermatitis the condition was classified in 13 as mild, in 10 as severe and in 2 as fatal. The type of lesion was erythematous in 10 instances, exfoliative in 7, macular in 4, maculopapular in 2, urticarial in 1 and scarlatiniform in 1. The interval between injection of the arsenical and appearance of the lesion varied from one hour to eight days. The length of time required for complete recovery varied from ten hours to fifty-seven days.

Rubner⁹³ presents an interesting report of a case of a patient 48 years of age who had a typical, apparently rather severe exfoliative dermatitis following the fifth injection of neoarsphenamine. Desquamation was complete about two months after the onset of the illness, and

92 Stephenson, C. S., and Chambers, W. M. Toxic Effect of Arsenical Compounds as Administered in the United States Navy in 1938, with Special Reference to Arsenical Dermatitis, *U. S. Nav. M. Bull.* **37** 687 (Oct.) 1939.

93 Rubner, M. Case of Melanosis After Salvarsan Dermatitis, *Acta dermat.-venereol.* **20** 502 (Aug.) 1939.

at that time the pigmentation of the skin was so pronounced that it was almost of a dark mole color. Only the nail beds and the mucous membranes were of normal aspect. From that point on, the general health improved rapidly, the hair and nails returned, but the melanosis remained unchanged. The author feels that in the absence of any of the usual causes of melanous deposits in the skin, arsphenamine dermatitis obviously provided the etiologic mechanism.

Erythema of the Ninth Day—Epstein and Levin⁹⁴ describe 6 patients in whom erythema of the ninth day developed after the injection of neoarsphenamine. In every case, arsenical therapy could be resumed without serious reaction. Grund⁹⁵ reports the third observed case of erythema of the ninth day following the intramuscular injection of a suspension of bismuth subsalicylate in oil.

Thrombopenic Purpura—Since their paper on the subject in 1936,¹⁶ Falconer and Epstein⁹⁶ have had the opportunity to study 5 additional patients in whom there developed thrombopenic purpura, in 2 after the administration of neoarsphenamine and in 3 after the administration of bismarsen. All were subsequently tested with mapharsen, and in none did there develop thrombopenia or purpura. The case of a sixth patient is reported, in whom hemorrhagic phenomena occurred without purpura or marked decrease in platelets.

The authors noted that varying degrees of shock occurred in the 5 patients with thrombopenic purpura after test doses of neoarsphenamine or bismarsen, and this, they believe, suggests that the reaction is an allergic phenomenon rather than one due to toxic effects of oxidation or to a changed chemical form of the drug injected. The loss of circulatory tone accompanying the reaction appears to be a vasomotor effect, with loss of capillary tonus, dilatation of the capillary bed and a rapid loss of platelets in the circulation. The authors feel that inasmuch as large numbers of platelets disappear from the blood within fifteen minutes after the injection of the arsenical compound, they are not destroyed, particularly since the return of many could be demonstrated soon after an injection of epinephrine. They do not consider the possibility that the platelets found after the injection of epinephrine may be a new supply liberated from the storehouses and not those originally observed.

94 Epstein, N. N., and Levin, E. A. Erythema of the Ninth Day Following Arsphenamine Therapy, *Am J Syph, Gonorr & Ven Dis* **23** 490 (July) 1939.

95 Grund, J. L. Erythema of the Ninth Day Following Bismuth Therapy for Syphilis, *Arch Dermat & Syph* **41** 1076 (June) 1940.

96 Falconer, F. H., and Epstein, N. N. Purpura Haemorrhagica Following Neoarsphenamine and Bismarsen Therapy. Further Studies on Sensitivity to Arsphenamine and Tolerance to Mapharsen, *Arch Int Med* **65** 1158 (June) 1940.

Hepatitis and Jaundice—Gott and Doyle⁹⁷ review in some detail 100 cases of jaundice which occurred in the course of antisyphilitic treatment of approximately 6,000 patients over a period of seven years in a large city hospital clinic. For the entire group the incidence rate for jaundice was 1.6 per cent, or 1 in each 62 cases, but in the group of 2,326 cases fairly regularly treated patients the incidence was 2.3 per cent, or 1 in each 44 cases. No woman under antepartum care or children under 12 years of age were included in the group. They found the incidence of recognized jaundice to be four times greater among the white than among the colored patients and three times as great in patients over 20 years of age as among those younger.

There was no apparent relationship between the stage of syphilis and the development of jaundice, although there was an apparent tendency for jaundice to develop early rather than late in the course of treatment. In this material the incidence of jaundice in patients whose treatment included mapharsen was approximately 10 per cent less than in those whose treatment included neoarsphenamine. The present authors feel that both the trivalent arsenical compounds and bismuth are hepatotoxic, the former being the more so. This toxicity is quantitative as well as qualitative, they feel, although there is evidence that the patient may develop some degree of tolerance for the drugs. In the cases of so-called delayed jaundice the arsenical and bismuth compounds may be used with comparative safety after the jaundice has subsided, and in any event the occurrence of jaundice has no effect on the ultimate clinical or serologic course of the disease, except insofar as it occasions modification of treatment.

Two patients in the present series died, the remainder recovered uneventfully and usually were able to tolerate further antisyphilitic treatment without serious consequences.

From the material available, the authors are unwilling to draw any conclusions concerning a possible etiologic relationship between so-called acute catarrhal jaundice and jaundice occurring during antisyphilitic treatment.

Snapper, Chin and Lin⁹⁸ report the case of a patient who died with acute hepatitis after he had received sixteen injections of neoarsphenamine totaling 7.4 Gm., ten injections of bismuth subsalicylate totaling 1.3 Gm. and one dose of 0.03 Gm. of mapharsen. At autopsy the liver was greenish yellow and was found to weigh 2,080 Gm., and microscopically

97 Gott, J. R., Jr., and Doyle, W. H. Jaundice During Antisyphilitic Treatment. A Survey of One Hundred Cases, *Internat. Clin.* 4: 153 (Dec.) 1939.

98 Snapper, I., Chin, K. Y., and Lin, S. H. Liver Degeneration Following Neoarsphenamine and Mapharsen Treatment, with Some Remarks on Catarrhal Jaundice and Arsenical Jaundice and Their Relation to Acute Yellow Atrophy, *Chinese M. J.* 56: 501 (Dec.) 1939.

there was extensive destruction of liver cells. The authors comment on the large size of the liver, apparently overlooking the fact that in acute toxic hepatitis the hypertrophic reaction of acute inflammation precedes atrophy, which is the result of escharotic resolution.

Rankin and Marlow⁹⁹ have investigated the question of residual damage to the liver recognizable at long intervals after arsphenamine jaundice in 24 patients. In all of the patients studied, hepatic damage, if present, was recognizable by means of laboratory tests only, there was no clinical evidence of cirrhosis.

Liver Function Test Retention of more than 5 per cent [of injected bilirubin] was present in 18 cases and of more than 10 per cent was present in 10 of 24 cases. Maximum retention was 26.8 per cent. None of these patients showed any evidence of slow blood flow.

Serum Bilirubin Level Five of 24 cases showed a level of greater than 0.8 mg per cent. Only one showed appreciable elevation to 1.5 mg per cent. This case also showed a bilirubin retention of 19.8 per cent.

Serum Proteins Some degree of abnormality was present in 12 of 23 cases, but change in more than one factor of total protein, albumin, or albumin-globulin ratio was present in only 8 of these. There was no correlation between these findings and the degree of bilirubin retention or other studies. None of these cases had edema.

Urobilinogen in Urine In 4 of 24 cases urobilinogen was present in greater than 1:20 dilution of freshly voided urine.

Erythrocyte Counts, Mean Corpuscular Volume, and Hemoglobin Concentration Five cases showed an abnormally high mean corpuscular hemoglobin above normal or at the upper limit of normal. While an anemia was not present, in each of these cases the erythrocyte count fell well below the findings in the remainder of the group. One case with alteration of mean corpuscular volume alone is not included in the statistics.

Radiography of the Liver In 22 of our cases 1 liver was small, 10 were large, and of the latter 3 were very large.

Infrared Photography of the Anterior Abdominal Wall In no instance among the cases studied was collateral circulation demonstrable by this method.

While the question of the influence of diet on the production of damage to the liver by arsphenamine is of major interest to clinicians, Messinger and Hawkins¹⁰⁰ reviewed the past experience of others to find conflicting claims coming from relatively similar experimental observations. They planned, therefore, a careful set of experiments with dogs. These animals were maintained on diets high in protein, carbohydrate or fat, as the case might be, for a period of at least a week before the first injection of arsphenamine and then, still maintained on the same

99 Rankin, T. J., and Marlow, F. W. Liver Damage After Recovery from Postarsphenamine Jaundice. A Follow-Up Study, *Am J Syph, Gonorr & Ven Dis* **24** 301 (May) 1940.

100 Messinger, W. J., and Hawkins, W. B. Arsphenamine Liver Injury Modified by Diet. Protein and Carbohydrate Protective, But Fat Injurious, *Am J M Sc* **199** 216 (Feb) 1940.

diets, were treated at weekly intervals for two to five weeks with doses of 0.03 to 0.05 Gm of arsphenamine per kilogram of body weight. The clinical status of the animals was followed during treatment, and at the end of the experimental observation either they were killed or a bit of liver was removed for biopsy.

It must be emphasized that the doses of arsphenamine used were very large, and, as might have been expected, sections of the livers of all the dogs showed that some injury had occurred. The diet high in protein content was found to be the most effective in protecting dogs against injury to the liver by arsphenamine, and such injury as occurred was trivial and promptly repaired. A carbohydrate diet was also beneficial but was not as uniformly protective, and the hepatic injury was frequently greater. In the experience of the present authors, fat proved to be deleterious, and on the fat diet under the otherwise standard experimental conditions dogs became intoxicated to the point of death.

In certain instances dogs that had been protected by protein or carbohydrate showed a progressive increase in the icteric index when changed over to the fat diet, even though no additional arsphenamine was injected.

When fat-fed dogs that showed severe intoxication due to arsphenamine injury were switched to protein or carbohydrate diets they immediately recovered from the intoxicated state and the icteric index decreased. Subsequent injections of arsphenamine caused no ill-effects as long as the dogs remained on either the protein or carbohydrate diet.

Soffer¹⁰¹ in discussing the treatment of postarsphenamine jaundice, concludes

- 1 When the clinical and experimental data presented in the literature concerning the treatment of arsphenamine jaundice are analyzed, one is impressed with the fact that a high carbohydrate diet is well accepted as an important therapeutic measure.

- 2 Such diets should consist of 400 to 600 Gm of carbohydrate per day divided into five or six feedings.

- 3 Those carbohydrate foods should be employed which are made up essentially of fructose and glucose, since these sugars are most readily converted into glycogen by the liver. Thus, cane sugar, which is hydrolyzed into glucose, honey, which is mostly glucose and fructose, and fruit juices are most desirable.

- 4 Where the amount of carbohydrate taken orally is inadequate, diets should be supplemented by a constant intravenous drip of 5 per cent glucose.

- 5 Insulin should be employed only when glycosuria is manifested.

- 6 The use of cholagogues and choleretics in the treatment of arsphenamine jaundice is an unsound form of therapy.

It is interesting that this continuing lack of agreement between clinical and laboratory experiences has inspired no effort to reconcile the two

¹⁰¹ Soffer, L. J. The Treatment of Postarsphenamine Jaundice, *Am J Syph, Gonorr & Ven Dis* **23** 577 (Sept.) 1939.

beyond Messinger and Hawkins'¹⁰⁰ statement of the problem. The laboratory workers deal with doses of arsphenamine which are admittedly hepatotoxic, while the clinician is concerned with the occasional development of damage to the liver after usual doses of an arsenical drug. Are the two flesh of the same fowl? It seems unlikely. Critical comparative investigation is required to solve this important problem. In the meantime, it seems fair to suggest that the diet best capable of protecting the liver against damage from the administration of arsenical drugs and that necessary for the preservation of essential metabolism when damage to the liver has occurred may not be the same and are probably widely different.

Hemorrhagic Encephalitis—Tzanck¹⁰² reports 5 cases of hemorrhagic encephalitis and summarizes the current consensus of the clinical picture. He brings out that the dose of the arsenical drug plays an unimportant part, that symptoms appear five to twelve days after treatment, that young persons are commonly affected, and that the reaction is not prone to develop in one sex more frequently than in the other, except so far as the incidence of hemorrhagic encephalitis is particularly high in pregnant women. He classifies the disease into severe, mild and abortive forms and says that 75 per cent of the patients with the severe form die.

Sodium Dehydrocholate as a Solvent for Neoarsphenamine—By experiments on rabbits Kolmer and Rule¹⁰³ demonstrated that neoarsphenamine dissolved in sodium dehydrocholate had the same therapeutic activity as neoarsphenamine of the same lot number dissolved in distilled water. As to the toxic effect of neoarsphenamine dissolved in sodium dehydrocholate, the authors say

In so far as its toxicity in rats is concerned, we have observed that the results of intravenous injections of single doses of neoarsphenamine dissolved in a 5 per cent solution of sodium dehydrocholate, 1 cc per kilogram of body weight, were practically identical with those of injections of corresponding amounts of neoarsphenamine per kilogram of body weight dissolved in sterile distilled water. In other words, comparative toxicity tests with three different lots of neoarsphenamine administered in the two menstrums showed practically identical maximum tolerated doses per kilogram of body weight.

It would seem, therefore, that while the use of a solution of sodium dehydrocholate as a solvent for neoarsphenamine is perfectly permissible, there may be some doubt that this maneuver accomplishes the desired purpose of reducing the toxicity of the arsenical drug.

102 Tzanck, A. Nomenclature et classification dermatologiques, *Ann de dermat et syph* **10** 752 (Jan) 1939.

103 Kolmer, J. A., and Rule, A. M. Influence of Sodium Dehydrocholate on Therapeutic Activity of Neoarsphenamine, *Arch Dermat & Syph* **41** 838 (May) 1940.

Reactions to Mapharsen—Rein and Wise¹⁰⁴ report 5 instances of blood dyscrasias occurring in the course of the administration of 2,342 injections of mapharsen to 113 patients. A fatal case of aplastic anemia is noteworthy as being the first reported instance of this reaction to mapharsen. The type of blood dyscrasia in the other 4 patients is not identified.

Reactions to Neosphenamine—Stephenson and Chambers¹⁰⁵ report the deaths and severe reactions following the administration of 1,244,537 doses of neosphenamine in the United States navy during the fourteen year period 1925 to 1938. There were 45 deaths, 16 due to hemorrhagic encephalitis, 12 to arsenical dermatitis, 6 to vasomotor phenomena, 6 to blood dyscrasias, 2 to acute renal damage, 2 to yellow atrophy and 1 to probable renal hemorrhage. Severe reactions without death totaled 294, of which 2 were due to hemorrhagic encephalitis, 187 to arsenical dermatitis, 56 to vasomotor phenomena, 18 to blood dyscrasias, 5 to acute renal damage, 18 to hepatic damage, 2 to Herxheimer reaction, 3 to gastrointestinal reactions, 1 to polyneuritis and 1 to optic neuritis, 1 was listed as due to arsenical neuritis.

Reactions to Tryparsamide—Kopp and Solomon¹⁰⁶ detail the reactions to tryparsamide which have occurred following the administration of 43,308 injections to 829 patients. Visual disturbances occurred in 4.5 per cent, progressing to optic atrophy in 1.2 per cent. In company with other workers¹ they have noticed an increasing incidence of the reactions more usually observed following the trivalent arsenical compounds. Their experience with nitritoid reactions is illustrative. During the first five years of tryparsamide therapy (1922 to 1926) only 1 patient had a nitritoid reaction. From 1928 to 1939 nitritoid reactions occurred each year except in 1932, and their incidence was 5.5 per cent in 1938 and 8.6 per cent in 1939.

The nitritoid reaction due to tryparsamide usually appears in the patient who has shown other manifestations of sensitivity, especially the gastrointestinal type of reaction. Other reactions common to this group of patients, and which in most instances have appeared prior to the nitritoid reaction, are chills, fever, fainting, weakness, dizziness, emotional upsets, drowsiness, and muscle tremors. The nitritoid reaction is also most apt to occur in a patient who has received considerable tryparsamide therapy. The reaction occurred in the course of the first

104 Rein, C. R., and Wise, F. Mapharsen in Treatment of Syphilis in Office Practice. A Study Based on 2,342 Injections of One Hundred and Thirteen Patients, *J. A. M. A.* **113** 1946 (Nov. 25) 1939.

105 Stephenson, C. S., and Chambers, W. M. Toxic Effects of Arsenical Compounds as Employed in the Treatment of Diseases in the United States Navy, 1938, *U. S. Nav. M. Bull.* **38** 126 (Jan.) 1940.

106 Kopp, I., and Solomon, H. The Untoward Reactions of Tryparsamide, *Am. J. Syph., Gonorr. & Ven. Dis.* **24** 265 (May) 1940.

ten injections in only 7 (17 per cent) of the 41 patients in this group, and after more than thirty injections had been given in 31 patients (76 per cent)

Gastrointestinal reactions were the most common, also recently have been more frequent and occurred in 59 or 71 per cent of the group. In only 6 patients, however, did gastrointestinal reactions appear before the tenth dose of tryparsamide.

Jaundice developed in 30 patients (36 per cent) and recurred in only 2 of the 30 after resumption of the treatment.

Numerous usually unimportant cerebral manifestations occurred, and dermatitis was observed in 8 patients and urticaria in 5.

The skin lesions have consisted of discrete or multiple desquamative patches, both large and small, on an erythematous base, red blotchy papules, and small purpuric-like areas. They have involved the wrists, fingers, arms, legs, shoulders, and forehead and are accompanied by pruritus. With omission of the drug, they have disappeared, with the exception of one case in which residual pigmented areas resulted following purpuric-like lesions. In 3 patients the dermatitis was of the fixed type already described in the literature and occurred after twenty-nine, thirty-one and thirty-four injections. The skin lesion recurred at the identical areas at a later date after a single additional injection. In 1 of the 3 patients the drug was continued in doses of 1 to 15 Gm in spite of the recurrence and the skin lesion disappeared only to reappear after thirty-two additional injections.

Levy¹⁰⁷ and Ellis¹⁰⁸ each add the report of a nitritoid reaction following the administration of tryparsamide, and Huber¹⁰⁹ describes 2 patients in whom dermatitis developed consequent to its use. In 1 patient the dermatitis was of the fixed type. The other patient had suffered an exfoliative dermatitis from a trivalent arsenical but had tolerated tryparsamide for some time before the skin reaction recurred.

In the course of a discursive article on the treatment of dementia paralytica, Wagner-Jauregg¹¹⁰ makes the statement that he has never seen toxic amblyopia to tryparsamide develop in a patient who previously had been treated with malaria.

Bismuth and Hepatic Necrosis—After pointing to the extreme rarity of hepatic disease following the administration of bismuth compounds, Wolman¹¹¹ reports the death of 2 infants from acute yellow atrophy of

107 Levy, H. A. Nitritoid Reaction to Tryparsamide. Report of a Case, *Arch Dermat & Syph* **41** 690 (April) 1940.

108 Ellis, F. A. Nitritoid Reactions Due to Tryparsamide, *Arch Dermat & Syph* **40** 707 (Nov) 1939.

109 Huber, W. M. Dermatitis from Tryparsamide, *Bull Genito-Infect Dis* **9** 3 (Dec) 1939.

110 Wagner-Jauregg, J. Derzeitige Behandlung der progressiven Paralyse, *Wien klin Wchnschr* **52** 1075 (Dec 1) 1939.

111 Wolman, I. J. Acute Necrosis of the Liver in Infants Following Sodium Bismuth Thioglycollate Administration, *Am J Syph, Gonorr & Ven Dis* **24** 330 (May) 1940.

the liver following the intramuscular injection of sodium bismuth thio-glycolate. Both were apparently normal infants with no clinical manifestations of syphilis, 1 received only one dose of the drug and died four days later. The other infant had received fourteen injections of sulfarsphenamine followed by ten injections of sodium bismuth thio-glycolate. Twenty-four hours after the last injection, the infant was hospitalized because of vomiting, dehydration and anuria and died a day later. The predominating lesion at necropsy was acute yellow atrophy of the liver in both infants.

INCIDENCE OF SYPHILIS

Following the report in 1888 by Gluck,¹¹² there was general acceptance that there existed in certain remote provinces, notably Bosnia, an endemic form of syphilis with characteristics strikingly different from those of the disease as seen in western civilization. This author described the regular absence of the primary sore, the rarity of early secondary lesions, the frequency of mucosal circumscribed cutaneous and late relapsing gummatous manifestations, the absence of pigmentary changes and lack of changes in hair or nails, the rarity of ocular involvement, the rarity of congenital syphilis, the ready response to treatment, and the frequent incidence of spontaneous cure.

After the publication of the report of the German-Russian expedition to Buryat-Mongolia,¹¹³ there began to arise some doubt as to the validity of Gluck's observations. The expedition found syphilis to be extraordinarily common, but not measurably to differ in its clinical manifestations from the disease as seen in the western world. The entire situation was therefore restudied, and, according to Kogoj,¹¹⁴ the only contention of Gluck's to be supported was that syphilis is endemic in Bosnia. Among 4,800 persons examined, 900 patients with syphilis were discovered. Primary lesions on the genitalia were rare, but four active extragenital primary lesions were found and numerous scars of such were noted, most often on the tongue. All known varieties of cutaneous syphilis were observed, and mucosal lesions outnumbered these. Gumma of the nasal septum was common. Without giving figures, this author states that the incidence of vascular syphilis, tabes dorsalis and dementia paralytica was much the same as that seen in the more sporadic variety of syphilis occurring in western civilization.

112 Gluck, L. Beiträge zur Kenntnis der Syphilis in Bosnien und in der Hercegovina, Wien med Presse **29** 993, 1033, 1105, 1137, 1170, 1202 and 1234, 1888.

113 Results of the Germano-Russian Syphilis Expedition, Foreign Letters, J A M A **96** 1162 (April 4) 1931.

114 Kogoj, F. Die endemische Syphilis in Bosnien und Herzegowina, Dermatologica **79** 361 (June) 1939.

Unfortunately, there are no accurate vital statistics in these remote districts on which to base figures for incidence and prevalence and no accurate records from which to determine the past course of the disease and its treatment in a patient who is seen only once late in the development of his syphilitic infection. It would seem wise, therefore, to reserve judgment on the possible differences or similarities between "primitive" and "civilized" syphilis until further and more searching study is available.

CONTACT INVESTIGATION

It has long been apparent to a few that the responsibilities of the physician regarding a patient with early syphilis do not end until the person who was the source of the infection has been identified and placed under treatment and any person exposed to the patient by sexual contact during his period of potential infectiousness brought under observation. With the development of syphilis control programs this fundamental epidemiologic approach has acquired the convenient name of "contact investigation," there is a developing recognition of its importance, and its use is becoming widespread. Obviously a great difficulty in the successful application of the method lies in the fact that it involves obtaining from the patient information (i. e., the name and address of the contact) which he considers private and would prefer to keep to himself. Clark¹¹⁵ suggests useful methods of circumventing the patient's diffidence, based on an approach which congratulates the patient on his good fortune in being under treatment for his disease and thereby freed from any blame of further transmitting it, and his responsibility to see that any person he knows or suspects to be in like condition is given a similar opportunity. The method is highly successful, as shown by Clark's experience in discovering early (and therefore potentially infectious) syphilis in 139 (two thirds) of 210 sexual contacts examined. This was from a group of 294 sexual contacts named by 242 patients with early syphilis and represents a ratio of patients with early syphilis discovered for each original patient investigated of approximately 53:100.

When the investigation was extended to nonsexual contacts, however, syphilis was discovered in only 17.3 per cent of those examined, which may represent primarily the basic incidence of the disease in the population with which he dealt.

Turner, Gelperin and Enright¹¹⁶ found that investigation of the contacts of 247 patients with early syphilis uncovered 114 previously

115 Clark, E. G. *Epidemic Syphilis: Its Recognition and Management by the Physician*, *Ann Int Med* **13**: 238 (Aug.) 1939.

116 Turner, T. B., Gelperin, A., and Enright, J. R. *Results of Contact Investigation in Syphilis in an Urban Community*, *Am J Pub Health* **29**: 768 (July) 1939.

unrecognized patients with the disease, of whom 74 had early syphilis, a ratio of patients with infectious syphilis to original patients of 30 100

These authors found, further, that the cost of investigating the contacts of a patient with early syphilis was about \$18. If this cost generally obtains, it would seem to limit the proper application of the method to sexual contacts, in which the returns are high, to the exclusion of household or family contacts, in which Clark found the returns to be much lower.

EARLY SYPHILIS

Infectiousness—Barnett and Kulchar¹¹⁷ undertook to determine whether *S. pallida* actually was present in the saliva of patients with infectious syphilis or whether its occurrence in the spittle merely reflected contamination from lesions in the mouth. Accordingly, saliva was obtained directly from the parotid ducts of 7 patients with untreated secondary syphilis and injected into the testes of rabbits. None of the animals acquired syphilis, and appropriate node transfers likewise gave negative results. The authors concluded, therefore, that the infectivity of saliva in patients with syphilis is probably due to contamination from lesions within the mouth.

By an ingenious technic, Vryonis and Morgan¹¹⁸ have made actual counts of the number of spirochetes contained in material from lesions of early syphilis. In 53 specimens from 39 patients, the concentration of spirochetes varied between 370 and 246,000 per cubic millimeter. The latter was in material from a genital condyloma, the former came from a healing secondary lesion on the dry skin. They conclude:

Our observations indicate that, if human beings are as susceptible to infection by *S. pallida* as rabbits, they may become infected by as little as $\frac{1}{375}$ cubic millimeter of condyloma fluid or $\frac{1}{150}$ cubic millimeter of chancre fluid.

Infectious Relapse—Pariser¹¹⁹ believes that although infectious relapse in syphilis usually occurs within the first two years of infection there are a significant number of patients who relapse after this time. In a brief period, he observed 6 of 120 treated patients with early syphilis to suffer infectious relapse two and a half years or more after infection. Of these 6 patients, 5 had received more than twenty injections of an arsenical compound and a corresponding amount of a heavy metal. Treatment, however, was irregular in 3 of the 5. Four patients had shown a tendency to early serologic reversal. The fact is stressed that

117 Barnett, C. W., and Kulchar, G. V. The Infectivity of Saliva in Early Syphilis, *J. Invest. Dermat.* **2** 327 (Dec.) 1939.

118 Vryonis, G., and Morgan, H. J. Spirochete Counts in Fluid from the Surface Lesions of Early Human Syphilis, *Ven. Dis. Inform.* **20** 343 (Nov.) 1939.

119 Pariser, H. Infectious Relapse in Syphilis of More Than Two Years' Duration, *J. A. M. A.* **113** 1206 (Sept. 23) 1939.

relapse may occur for many years after the initial infection and that intermittent treatment predisposes

Osteitis—Although only a few reported cases of osteitis occurring in early syphilis can be found in the literature, the condition is by no means rare. It is overlooked simply because skeletal roentgenograms are not taken routinely for patients with early syphilis. Wile and Welton¹²⁰ remark on this and report 2 cases in which the bones were involved as a result of early syphilis. In 1 case the condition clearly simulated multiple myeloma.

Hepatitis—Creswell, Golden and Coakley¹²¹ report 2 cases of acute syphilitic hepatitis in patients with early syphilis. Both patients tolerated treatment with 60 mg of mapharsen weekly, and recovery was uneventful.

Treatment-Resistant Syphilis—Beckh and Kulchar¹²² note that in the European literature considerable attention has been paid to treatment-resistant syphilis but that reports are few from this country. In classifying treatment resistance into three groups as (1) primary (i.e., failure of the original lesion to heal), (2) primary-secondary ("when the initial lesions were treatment-resistant but eventually involuted, and later there were refractory recurrences during treatment") and (3) secondary (with the occurrence of treatment-resistant relapse during treatment), the authors placed 3 of their 18 patients in the first group, 2 in the second and the remaining 13 in the third. Experience with these patients led them to feel that the factors involved in treatment resistance may be grouped as involving the host, the spirochete or the drug, either singly or through an interaction of two or more factors. In their opinion there is no evidence to support the concept of a treatment-resistant strain of the spirochetes and there is very little evidence on which to base an assumption that variations in the host reaction explain the phenomenon of treatment resistance. Likewise, since the patients in their series were treated with drugs of the same lot which was effective in the management of other patients, the authors feel that variation in the quality or potency of the drugs employed may be excluded as an etiologic factor. They emphasize, however, that in 7 of the 11 patients who were treated with neoarsphenamine and on whom the data are complete, and in 2 of the 3 patients who were treated with mapharsen, the dose of these

120 Wile, U. J., and Welton, D. G. Early Syphilitic Osteomyelitis with Report of Two Cases, *Am J Syph, Gonorr & Ven Dis* **24** 1 (Jan) 1940.

121 Creswell, G. W., Golden, R. F., and Coakley, C. S. Acute Benign Syphilitic Hepatitis. Report of Two Cases, *M. Ann. District of Columbia* **8** 303 (Oct) 1939.

122 Beckh, W., and Kulchar, G. V. Treatment-Resistant Syphilis. An Evaluation of the Causative Factors in Eighteen Cases, *Arch. Dermat. & Syph* **40** 1 (July) 1939.

trivalent arsenical drugs administered was inadequate. They properly conclude, therefore, that the high incidence of so-called treatment resistance observed among patients receiving combined therapy (i.e., simultaneous treatment with an arsenical compound and a bismuth preparation) which was evident in their series is due to prolonged underdosage with the trivalent arsenical compound. They do not, however, clearly distinguish between treatment resistance and relapse due to inadequate treatment, especially in the patients in group 3, in 9 of whom manifestations came on after as long as forty months to six years of observation and treatment.

Massive Dose Method of Treatment—Since last year's review, the Mount Sinai group¹²³ have added other papers on the massive dose method of treatment. In addition, on April 12, 1940 there was held in New York an invitation meeting at which the most recent results from the use of the method were presented. From this meeting came a wave of newspaper publicity which had the "five day cure" in headlines all over the country, with the consequent unfortunate creation of demands from patients with all types of syphilis that the treatment be administered. An editorial commentator¹²⁴ summarizes the present status.

The results of Hyman and his collaborators suggest that what is true of sulfanilamide and bacterial infection also may be true of arsenic and syphilis. It is important to point out, however, that much further study is essential before the method under trial by the Mount Sinai Hospital group can receive general application.

There are as yet inadequate data as to the toxicity of such large doses of arsenical drugs given by this method. In human beings and using neoarsphenamine in the arbitrarily selected dose of 4 to 5 gm, there was a high incidence of reactions, especially polyneuritis (35 per cent). It is desirable exactly to redefine in experimental animals the minimum lethal and maximum tolerated doses with the new technique.

It is further desirable to redefine with the new method the minimum curative dose in experimental rabbit syphilis. With the usual single injection technique, the curative dose of arsphenamine is 10 to 12 mg/kg, with neoarsphenamine, 15 to 25 mg/kg, with mapharsen the minimum curative dose is not definitely known, but it is certainly less than 6 mg/kg, perhaps as little as 2 to 3 mg/kg.

123 Chargin, L., Leifer, W., and Rosenthal, T. Mapharsen in the Treatment of Early Syphilis. Comparison of Results in One Hundred and Eighty-Eight Cases with Those of the Cooperative Clinical Group, *Arch Dermat & Syph* **40** 208 (Aug.) 1939. Hyman, H. T., Chargin, L., Rice, J. L., and Leifer, W. Massive Dose Chemotherapy of Early Syphilis by the Intravenous Drip Method, *J A M A* **113** 1208 (Sept 23) 1939. Hyman, H. T., Chargin, L., and Leifer, W. Massive Dose Arsenotherapy of Syphilis by the Intravenous Drip Method, *Am J Syph, Gonorr & Ven Dis* **23** 685 (Nov.) 1939.

124 The Massive Dose Arsenotherapy of Early Syphilis, editorial, *Am J Syph, Gonorr & Ven Dis* **23** 797 (Nov.) 1939.

The clinical studies already carried out suggest that by the continuous intravenous drip method minimum curative doses will be found to be much smaller. From the standpoint of toxicity, moreover, it is important to determine experimentally not only that animals will survive the injection of the minimum curative dose, but also, by necropsy of animals so treated at varying intervals thereafter, that permanent damage to important tissues is lacking.

Since the clinical studies suggest that curative effect depends on moderate prolonged blood concentration of the treponemicidal substance, it is clear that this in turn depends on the inter-relationship of dosage and time of administration. Studies in experimental animals, while not directly transferable to syphilis in man, nevertheless will permit a more exact definition of these relationships. Such studies may show that comparable clinical results may be accomplished in a still shorter time than the apparently arbitrarily chosen five days or with a smaller and therefore perhaps safer dosage level than those so far arbitrarily selected.

The all-important time-dose relationship should be checked not only by studies in experimental animals but also by chemical studies of excretion (already in progress) and blood and tissue concentration in man.

Nothing is known as yet of the possible effects of this method of treatment in various forms of late syphilis. It is generally thought that one reason for the less satisfactory curative results (in the biologic sense) of treatment in late as compared to early syphilis lies in the fact that in the late stages of the disease the organisms tend to localize in tissues which the relatively poorly diffusible trivalent arsenical drugs fail to reach in treponemicidal concentration.

This consideration, together with the fact that in bacterial infections sulfanilamide and its derivatives owe much of their success to their extremely rapid diffusibility to all tissues of the body, suggests that the trivalent arsphenamines, which are semicolloids possessing relatively poor properties of tissue penetrability, presumably because they combine with serum proteins to form complexes which are either inactive, nondiffusible, or both, may be much less suitable drugs for this method of treatment than the arsenoxides, which probably do not so combine and which are therefore theoretically more readily diffusible. Indeed, it is still further suggested that other drugs, much less effective than either the arsphenamines or arsenoxides when administered by the conventional technique, may prove to be superior by the new method because of the factor of increased diffusibility.

As yet, therefore, not only are the factors of dosage and the proper duration of treatment unsettled, but it is not yet certain that the most suitable drug or group of drugs for this particular technique has been found.

From the immediate practical standpoint, finally, it must be emphasized that the method is one which necessitates at least one week of full hospitalization, that its dangers have not yet been accurately defined, and that seventy-eight of the ninety-three patients so far reported have been followed for only one year after treatment, an interval too short to determine the permanency of results.

While the method is therefore still in the experimental stage and unsuitable for mass application, it may prove nevertheless to be of major importance both to the individual patient and the public health. Further intensive study is amply justified.

Supersensitive Serologic Tests as a Guide to Cure—In the search for some standard by which to guide treatment following the disappointing discovery that one dose of arsphenamine would not cure syphilis in

the human being as it does in the rabbit, the clinicians of an earlier day naturally turned to the Wassermann reaction. They were disappointed again, at least in the sense that it was soon apparent that the obvious course of treating only until the reaction gave a negative result might be followed by disastrous relapse in the patient with early syphilis. Serologists ever since, however, have dreamed of developing a test a negative result from which could be used as a measure of cure. Levine, Littman and Kline¹²⁵ relate an attempt to use the Kline exclusion test in such a fashion. For this study the authors selected 44 patients with primary secondary or early congenital syphilis. Weakly or strongly positive reactions to Kline exclusion tests were obtained at or shortly after admission in those tested, and treatment was stopped when at least three consecutive exclusion tests, made a week or more apart, gave negative results and the cerebrospinal fluid was normal. The average period of treatment for the group was twenty-three months, the minimum was five weeks, and the maximum was five years. Followed for from eight months to twelve years (37 for two years or more), all patients were found at their last examination to be free from any sign or symptom of syphilis.

The danger of relapse in the patient whose treatment is stopped as soon as seronegativity is attained is obvious. Not so obvious, but equally undesirable is the inevitable gross, unnecessary prolongation of treatment which too frequently would follow the use of this "test of cure." In expert hands^{1a} the Kline exclusion test may give almost 10 per cent false positive or doubtful reactions in normal persons, in routine use the proportion may be much higher. This means that, purely mathematically, the dice are loaded against any one's being able to line up three consecutive negative results to this test in the average sero-diagnostic laboratory, irrespective of whether he has syphilis or not, or if he has, of the amount of preceding treatment for it and the need for more.

The crux of the matter seems to lie in the confusion of thought reflected by the authors in their discussion of the use of the Kline exclusion test in the early diagnosis of primary syphilis.

Rather than forego the use of these important very sensitive blood tests, their interpretation should be put on the same basis as that of the specific Widal test in an early suspected case of typhoid fever.

The fallacy of that statement is readily apparent. The Widal test is performed with a suspension of the *causative organism* as the antigen, in the Kline test the antigen is an extract of *beef heart*. No fundamental

125 Levine, B., Littman, S., and Kline, B. S. Syphilometry with the Exclusion Slide Tests in Forty-Four Cases of Early Treated Syphilis, *Am J Syph, Gonorr & Ven Dis* **23** 413 (July) 1939.

specificity for such an antigen can be claimed, the high order which has been achieved is entirely empiric, and there is now ⁴⁰ convincing evidence to indicate that "beef heart-fixing" reagin and "spirochete-fixing" reagin are not identical

Kemp ¹²⁶ calls attention to the practical implication of the concept of immunity in syphilis to the practicing physician. The most important point brought out is that the element of time is an important factor in the development of immunity in syphilis and that treatment started before the immune response is fully established may abruptly terminate or at least disturb its development. It is also true that immunity developed after inadequate treatment is inferior to the immunity developed in the untreated patient. The physician treating early syphilis must realize the responsibility placed on his shoulders.

The Prognosis of Early Syphilis—Utilizing the "questionnaire by mail" method of investigation, Willners ¹²⁷ sought to trace and determine the status of 616 patients with early syphilis who were treated during the years 1912 and 1913. It was possible to obtain some information regarding 256 patients in this group, of these, 116 (45.3 per cent) were dead, 121 (47.3 per cent) were living, free from symptoms, according to declarations either by themselves or by their physicians, and 19 (7.4 per cent) were living but were ill from syphilis or some other disease. Assuming that the mortality among the untraced patients was equal to that among the traced, Willners records an excess mortality of 32 per cent over the death rate for adults in Stockholm in the period under consideration. In analyzing the causes of death, however, Willners gains the impression that this excess death rate is much more due to other factors. It is unfortunate that from the nature of the study there is little evidence regarding the actual status of the living patients.

In the course of a discussion of the prognosis of treated syphilis Lomholt ¹²⁸ remarks on a series of 538 men with early syphilis who had been under observation after treatment for from fourteen to twenty-three years. Treatment had been begun during the primary stage in 217 patients and during the secondary stage in 321 patients. Dementia paralytica eventually developed in 3 of the former and 15 of the latter.

The author's main point is that a negative result on examination of the cerebrospinal fluid a year after the suspension of treatment for early syphilis gives, for all practical purposes, assurance against the development of neurosyphilis in the future.

¹²⁶ Kemp, J. E. Practical Considerations of Immunity in Syphilis, *M. Ann. District of Columbia* **9** 37 (Feb.) 1940.

¹²⁷ Willners, G. A Re-Examination of Cases of Fresh Syphilis Treated in 1912-1913, *Acta dermat.-venereol.* **20** 463 (Aug.) 1939.

¹²⁸ Lomholt, E. The Prognosis of Treated Syphilis, *Acta dermat.-venereol.* **20** 482 (Aug.) 1939.

LATENT SYPHILIS

According to O'Leary,¹²⁹ latency may be defined as that period of syphilitic infection after the disappearance of the signs of acute syphilis when the patient is free from both signs and symptoms of the disease and the cerebrospinal fluid is normal. He emphasizes that the therapy of latent syphilis cannot be systematized and feels that if the disease has been present for thirty or forty years treatment is not warranted but that if the stage of latency has only recently been attained treatment should be as for early syphilis. Since the great bulk of patients who have latent syphilis lie between these extremes, decisions regarding treatment must be individualized.

There is a general tendency to assume that patients with latent syphilis suffer nothing but the existence of the positive result to a laboratory test. Cormia and Lewis¹³⁰ correct this fallacy by demonstrating that apparently latent syphilis may produce symptoms without demonstrable involvement of any vital organ.

LATE SYPHILIS

Syphilis of the Thyroid Gland—Riecke¹³¹ reports the cases of 2 patients with gumma of the thyroid and partially reviews the literature on the subject. His patients were women 41 and 54 years of age respectively. The first came under observation because of the symptoms of tracheal obstruction, at operation a large mass was found to arise in the right lobe of the thyroid and to invade the trachea by direct extension, with consequent stenosis. On histologic examination this mass was found to be a gumma, subsequently the patient was found to have a positive serologic reaction for syphilis, and treatment was instituted with bismuth. The second case was similar to but less dramatic than the first, the diagnosis was suspected because of the experience with the first case, and a serologic test for syphilis was made with positive results before operative intervention. Operation was necessitated, however, by virtue of the respiratory obstruction.

From an incomplete review of the literature, the author concludes that there are at least four varieties of syphilis of the thyroid gland, the nature and severity being dictated by the incidental features of the individual case. In early syphilis, generalized invasion of all of the tissues does not spare the thyroid, but this is usually quite symptomless

129 O'Leary, P. A. Lues Latens, *New England J. Med.* **221** 764 (Nov. 16) 1939.

130 Cormia, F. E., and Lewis, J. A. Interpretation of the Factor of Latency in Syphilis, *Canad. M. A. J.* **42** 154 (Feb.) 1940.

131 Riecke, H. G. Syphilis der Schilddrüse, *Dermat. Wchnschr.* **110** 1 (Jan. 6) 1940.

Occasionally, however, there have been reports of acute thyroiditis, apparently due to syphilis, in patients with recently acquired syphilitic infection. Still others have described a diffuse syphilitic interstitial thyroiditis which is somewhat unconvincing, and finally, as in the present cases, the thyroid may present the localization for a gumma which differs not at all from gumma arising elsewhere.

Traumatic Syphilis—"By traumatic syphilis," says Higoumenakis,¹³² "we understand open syphilitic lesions which appear on a wound after a violent traumatism of the soft parts, which often causes lesions of the subjacent bone, or after repeated micro-traumatisms (contusion)." With that somewhat unclear definition of traumatic syphilis, the author proceeds to an extensive review of the older literature and the report of 6 personally observed cases in which there seemed to be a relationship between trauma and the development of lesions of syphilis. In contrast to some of the previously reported cases, those of the present series are relatively unconvincing, but from the literature and these observations the author concludes

(1) Every traumatic ulceration which adopts specific clinical characteristics or more simply which does not have any tendency to cicatrize, in spite of proper treatment, must cause us to suspect a syphilis which was not diagnosed, either acquired or hereditary, or a syphilis which was treated irregularly or insufficiently. In these cases, one must make a Wassermann reaction and if necessary one should make an experimental treatment.

(2) Almost always, one succeeds in demonstrating that such patients suffer from acquired or hereditary syphilis which was not diagnosed or of [sic] syphilis which was treated insufficiently and irregularly.

(3) The traumatic ulcerations which resist the usual treatments retrocede almost always after experimental anti-syphilitic treatment, when it is conducted according to the rules and when the traumatic ulceration has already transformed itself into a syphilitic lesion.

Syphilis as a Cause of Elephantiasis of the Lip—Netherton and Curtis¹³³ call attention to a rare manifestation of late syphilis which was described by Fournier under the title of diffuse hypertrophic syphiloma. There is swelling which is usually limited to the lower lip, although it may involve only the upper or both. The lips retain their general form, but the involved lip appears to be rolled outward. There is neither accompanying lymphadenopathy nor pain. Fournier observed late cutaneous syphilids involving the nose and skin in some of his patients. In his hands treatment with the iodides and mercury resulted in improve-

132 Higoumenakis, G. C. Contribution to the Study of Traumatic Syphilis, *Indian J. Ven. Dis.* **5** 141 (June-Sept.) 1939.

133 Netherton, E. W., and Curtis, G. H. Elephantiasis of Lips and of Male Genitalia, with Special Reference to Syphilis and Lymphogranuloma Venereum as Etiologic Factors, *Arch. Dermat. & Syph.* **41** 11 (Jan.) 1940.

ment but not cure. The present authors report the lesion in 2 patients, who are in every way typical, there was no improvement under treatment.

In discussing the implications involved the authors say

Although this condition has been reported as occurring only in syphilitic persons, there is reason to doubt that syphilis is the true cause. The rarity of the disease precludes an extensive investigation of this problem by a single observer. All observers have based their opinions regarding the nature of Fournier's diffuse hypertrophic syphiloma on clinical findings. So far as we have been able to determine, no one has studied the pathologic character of this condition, and until some one is able to obtain tissue for histologic examination the nature of the hypertrophy will remain obscure.

CARDIOVASCULAR SYPHILIS

Incidence—Perry and Langsam¹³⁴ present a clinical and necropsy study of fatal cardiovascular disease which is based on a series of 877 autopsies. Of this number, 334 (39.2 per cent) showed evidence of cardiovascular disease, and in 243 instances it had been the cause of death. Of all the patients who showed evidence of vascular syphilis, however, only 37 per cent died as a result of that condition. The authors point out the difficulty of attempting to transfer this comparison to living patients.

Cause of Cardiac Hypertrophy—Strong and Munroe¹³⁵ found 42 hearts weighing 750 Gm or more in 1,372 autopsies. The enlargement was due to syphilitic aortic insufficiency in 7 instances.

Association with Bacterial Endocarditis—To the 11 proved cases of vegetative bacterial endocarditis superimposed on syphilitic aortic valvulitis, Braunstein and Townsend¹³⁶ were able to add 9 others. Analysis of the clinical, bacteriologic and pathologic data available for these 20 cases forms the basis of their report.

The clinical and pathologic observations in 20 cases of bacterial endocarditis superimposed on syphilitic aortic valvulitis have been analyzed. Two types of endocarditis exist, acute and subacute [7 and 13 cases respectively]. Both, though similar to the usual type of endocarditis, do present certain differences.

In cases of the acute type there was a marked prevalence in men. In all the cases of this type there was positive evidence of syphilis and absence of a history of rheumatic fever, marked dyspnea was present at the onset of the illness, and

134 Perry, T. M., and Langsam, S. M. A Study of Cardiovascular Disease in Charleston, S. C., Based upon Necropsy Statistics, *Am Heart J* **19**:424 (April) 1940.

135 Strong, G. F., and Munroe, D. S. Cardiac Hypertrophy. Forty-Two Hearts Weighing Seven Hundred and Fifty Grams or More, *Ann Int Med* **13** 2253 (June) 1940.

136 Braunstein, A. L., and Townsend, S. R. Bacterial Endocarditis Superimposed on Syphilitic Aortic Valvulitis, *Arch Int Med* **65** 957 (May) 1940.

there were typical signs of syphilitic aortic valvular insufficiency and septicemia. At autopsy the aortic valvular vegetations were described as large in most of the cases in which the size was mentioned. There were syphilitic aortitis, valvulitis, aortic insufficiency and cardiac hypertrophy in all. No changes due to rheumatic fever were present in any cases.

In the cases of the subacute type there was also a marked prevalence in men, and there was positive evidence of syphilis and absence of a history of rheumatic fever in all the cases in which this point was mentioned, no chills, chilly sensations or subjective sense of fever were reported in most of the cases, there was progressive dyspnea early in the disease, with peripheral edema setting in about two months later, reduced incidence of petechiae, embolic phenomena and nephritis, there were no changes in the color of the skin of the white patients, typical syphilitic aortic valvular insufficiency was present, and the course was typically one of cardiovascular syphilis with signs of myocardial failure (left ventricular) predominating and endocarditis appearing subdued. Postmortem examinations revealed syphilitic aortitis, valvulitis and aortic insufficiency in all the cases, cardiac hypertrophy was pronounced, the average cardiac weight being greater than in the cases of rheumatism with aortic valvular bacterial endocarditis. In our cases the vegetations were noted on the *ventricular surfaces and bases* of the valves and not on the occlusal margins, the vegetations were small, with a marked tendency toward healing, destruction or distortion of the aortic cusps was not mentioned in any case, there was no evidence of rheumatic changes in any of the cases (i e, in the valves and myocardium).

From the analysis of the bacteriologic studies it was found that in most of the cases acute endocarditis was caused by pyogenic organisms. In 1 case it was caused by a nonhemolytic streptococcus. In 2 cases materials taken for cultures repeatedly showed no growths, and in 1 case no cultures were made.

In the cases of subacute endocarditis *Str. viridans* was observed in materials taken for culture *intra vitam* in 2 cases and *post mortem* in 2 cases. A non-hemolytic streptococcus was observed in materials taken for culture *post mortem* in 1 case. In 2 cases cultures (*intra vitam*) repeatedly gave negative results, and in 6 instances no material was taken for culture.

The diagnosis of the simultaneous presence of both conditions is admittedly difficult, since not many clues are present to arouse suspicion of the existence of bacterial endocarditis. Aortic insufficiency will in most instances be readily perceived. Subacute endocarditis, however, will in most of the cases manifest itself only by a gradual progressive anemia, associated with slight daily intermittent rises in temperature, to 100 or 101 F. Without other explanation for these conditions (fever and anemia) bacterial endocarditis superimposed on syphilitic aortic valvulitis must be suspected, and blood cultures should be made repeatedly if negative results are given. (In practically all of our cases the temperature elevation was thought to be due to terminal pneumonia, while the anemia, in most instances, was ignored.)

When the evidences of subacute endocarditis are more outspoken (i e, embolic phenomena, petechiae and nephritis), then the diagnosis becomes simpler, but it must be remembered that these frank forms of subacute bacterial endocarditis are only occasionally (as far as we could make out) implanted on syphilitic aortic valves. Most frequently they are located on rheumatic or normal valves, and the occurrence in these cases of positive Wassermann reactions would tend to throw one off the right track. In the presence of definite syphilitic aortic insufficiency, bacterial endocarditis, if obvious, is most likely to be situated on a valve other

than the aortic. This will probably be true in most cases, even though it may be known that syphilitic aortic insufficiency has existed for a long time before the present illness.

Association with Rheumatic Heart Disease—Swanson¹³⁷ found only 30 reported cases of the combination of rheumatic heart disease and syphilitic aortitis, and of these only 14 were authenticated. A study of 1,841 autopsies revealed 4 additional instances of the coincidence of the two diseases among 57 patients with some form of cardiovascular syphilis and 48 patients with active or inactive rheumatic heart disease. Concerning the possibility of establishing the correct diagnosis during life, the author says:

Clinically, it is often impossible to establish the diagnosis of combined rheumatic heart disease and syphilitic aortitis. In three cases in this series this was true, and the diagnosis was made only at autopsy. However, in Case 1, the presence of aortic stenosis associated with clinical and roentgenologic evidence of aneurysm of the aorta and a positive blood Wassermann reaction made it possible to establish the correct diagnosis. This particular combination of the two lesions, and cases of aneurysm of the aorta with mitral stenosis and without aortic insufficiency are probably the only two combinations in which the diagnosis can be made with certainty clinically.

Levitt and Levy¹³⁸ also report the case of a patient with rheumatic mitral endocarditis and syphilitic aortitis.

Association with Rupture of the Aorta—Galbraith and Hardwick¹³⁹ report the case of a patient who suffered spontaneous rupture of the aortic wall without the development of a dissecting aneurysm. Post-mortem examination revealed syphilitic aortitis, a defect in the intrapericardial portion of the aorta and the pericardium enormously distended with blood. The description is so typical of aortic rupture at this site due to the mechanism by which dissecting aneurysm occurs that one might hesitate to accept syphilis as the sole etiologic agent.

Pathogenesis of Aortic Insufficiency—In a study which is of great importance to an understanding of the mechanism by which aortic insufficiency develops, Wilens¹⁴⁰ determined how much variation in the amount of elastic tissue may occur in nonsyphilitic aortas and whether

137 Swanson, H. Combined Syphilitic and Rheumatic Disease of the Heart. Report of Four Cases, *Am Heart J* **18** 672 (Dec) 1939.

138 Levitt, A., and Levy, D. S. Syphilitic Aortic Disease. An Analysis of Five Hundred and Eight Cases, *New York State J Med* **40** 648 (April 15) 1940.

139 Galbraith, A. J., and Hardwick, S. W. Spontaneous Rupture of the Aorta. Direct Rupture of the Aorta Simulating Dissecting Aneurysm, *Am Heart J* **19** 100 (Jan) 1940.

140 Wilens, S. L. Relation of the Elastic Tissue in the Root of the Aorta to the Aortic Valve. Involvement of This Tissue in Syphilis, *Arch Path* **29** 200 (Feb) 1940.

it is of sufficient magnitude to shield or expose the cusps in the event of syphilitic inflammation. Comparative measurements were made on 73 nonsyphilitic adult hearts and 45 syphilitic aortas, in 24 of which aortic regurgitation had developed. He concludes

Measurements on the nonsyphilitic aorta reveal that the elastic tissue of the media at the root may project a variable distance proximal to the commissural attachments of the aortic valve cusps and that the lateral attachments of the cusps may show a great deal or very little of the medial coat in the wall of the underlying aorta. These variations do not appear to be related to the size of the aorta or heart and are not influenced by age, sex, body length or heart weight.

Since the lateral attachments of the aortic cusps are chiefly involved in the development of aortic insufficiency due to syphilis, it is pointed out that the degree of valvular damage may depend in part on the extension of the media in this area.

Measurements on the syphilitic aorta support this concept. The elastic tissue of the media is found to end more abruptly at the commissures in cases in which aortic insufficiency has failed to develop than in cases in which the valves are incompetent.

The three commissures in the normal aorta have different amounts of elastic tissue in their walls. Although the relative degrees of involvement of each of the three commissures varies in individual cases, in a series of cases of syphilitic aortitis with aortic insufficiency the average degree of involvement varied directly with the amount of intramural elastic tissue.

The highest point of attachment of the aortic cusps is found to be lower in the syphilitic aorta than in the normal one. This displacement is not related to changes in the leaflets themselves, since it is found when the cusps are still delicate and normally inserted.

Bellet and his associates¹⁴¹ bring out that while the diastolic murmur of aortic regurgitation is usually soft and blowing in quality, occasionally it may be strikingly musical and very loud. Numerous explanations for the mechanism of the production of such murmurs have been advanced, but most recent observers have come to regard a ruptured or torn leaflet as practically the only or at least the usual cause of this finding, in spite of the fact that in his original description, in 1829 Hodgkin associated the murmur with retroversion or eversion of a valve leaflet. Bellet and his group have observed 11 patients with this so-called "dove-cote" murmur, 6 of them came to postmortem examination. Of the latter, syphilis was the cause of the disease in all, and in all there was retroversion of the right anterior aortic valve leaflet. By the term "retroversion" the authors mean that at some point distal to the attachment of a leaflet to the aortic walls pathologic processes have caused the distal portion of the valve to become bent downward toward the chamber of the left ventricle. The mechanism by which this is produced

¹⁴¹ Bellet, S., Gouley, B., Nichols, C. F., and McMillan, T. M. Loud, Musical, Diastolic Murmurs of Aortic Insufficiency. Clinical and Pathologic Observations upon Their Cause and the Mechanism of Their Production, *Am Heart J* 18 483 (Oct) 1939.

is not clear, it may in some instances be the result of bending of the valve over a thick, tense, fibrous band running the length of the leaflet parallel to the free margin, and the authors suggest that loss of the support normally furnished by the elastica may be a contributing factor. They think it probable, however, that a number of factors contribute. They are properly unwilling to draw sweeping conclusions on the basis of so small an amount of material, but their study emphasizes that current consensus must be revised and proper place given to retroversion of an aortic cusp in the production of this characteristic murmur.

Epstein's¹⁴² studies would indicate that arteriosclerotic changes in the aorta and aortic valves alone rarely produce the characteristic murmur of the aortic regurgitation.

Aneurysm—Of the 224 patients with aortic aneurysm whose cases were analyzed by Collins,¹⁴³ only 155 (69.2 per cent) were found to have syphilis. This incidence of syphilis is lower than that usually observed and would raise the question of the case with which syphilis was excluded in the cases of the presumably nonsyphilitic group.

Valsalva treated aneurysm by venesection and restriction of fluids, and Marzullo¹⁴⁴ reports an interesting case in which his treatment was similar. Fourteen months after seven venesections of 500 cc each at intervals of three or four days and the administration of phenylhydrazine, roentgen examination showed complete calcification of the aneurysmal sac.

Aneurysm of the Pulmonary Artery—Boyd and McGavack¹⁴⁵ point out that the role of syphilis in the production of aneurysm of the pulmonary artery has been a matter for dispute. From 2 personally observed cases and a review of 109 others reported in the literature, however, they conclude that approximately a third of the aneurysms are syphilitic in origin.

Intracranial Aneurysm—The study by McDonald and Korb¹⁴⁶ confirms the general impression that syphilis uncommonly is the cause of intracranial aneurysm. Bassoe's¹⁴⁷ experience is in agreement regard-

142 Epstein, B. S. Comparative Study of Valvular Calcifications in Rheumatic and in Nonrheumatic Heart Disease, *Arch Int Med* **65**:279 (Feb.) 1940.

143 Collins, D. C. Aneurysms of the Aorta, *Mil Surg* **86**:270 (March) 1940.

144 Marzullo, E. R. Aneurysm of the Aorta. Report of a Case with Apparent Complete Recession, *New York State J Med* **40**:292 (Feb. 15) 1940.

145 Boyd, L. J., and McGavack, T. H. Aneurysm of the Pulmonary Artery. A Review of the Literature and Report of Two New Cases, *Am Heart J* **18**:562 (Nov.) 1939.

146 McDonald, C. A., and Korb, M. Intracranial Aneurysms, *Arch Neurol & Psychiat* **42**:298 (Aug.) 1939.

147 Bassoe, P. Aneurysm of the Vertebral Artery, *Arch Neurol & Psychiat* **42**:127 (July) 1939.

ing the small aneurysms of the circle of Willis, but he feels that the larger aneurysms of the vertebral and basilar arteries more frequently may be due to syphilis

Roentgenologic Examination in Diagnosis of Syphilitic Aortitis—There has been an unjustified tendency to feel that routine roentgenologic examination is of great value in determining the presence of syphilitic aortitis. Speaking from the experience of a competent radiologist, Sussman¹⁴⁸ says

Well defined deviations from the normal in size of the aorta yield evidence of disease. Our methods of measurement do not permit of precise determination of minor deviations, particularly in the ascending portion. Experience in roentgenoscopy of the chest, particularly as it permits observations of the variations in the great vessels due to the position of the diaphragm, of posture, of chest deformity and of age, has appeared more valuable than rigid application of mensuration. The smaller the deviation from normal the less valuable and sometimes more confusing is the information obtained. The roentgen examination of the aorta may not prove particularly valuable in the early diagnosis of luetic aortitis.

It is my impression that as regards the two great vessels, if the roentgen findings are considered alone and completely apart from the clinical data, the value of the examination has been overestimated in the literature. In actual practice it has its definite place when considered as an integral part of the physical examination.

NEUROSYPHILIS

Diagnosis—Prendergast¹⁴⁹ provides a general discussion of the problems presented by dementia paralytica and concludes with a strong plea for routine examination of the cerebrospinal fluid in every patient with syphilis. Concerning this he says

I do not propose to follow this question in greater detail, because to do so would require a lengthy article in itself, my sole object is to urge strongly the routine lumbar puncture of every syphilitic and so to avoid what we have repeatedly seen in patients arriving at Mont Park the development of typical general paralysis when the patient is actually undergoing intensive arsenic and bismuth therapy.

To medical men who are not accustomed to dealing with paretics, it may seem that an unnecessary fuss is being made about a relatively infrequent disease. When it is remembered that almost every case of general paralysis brings with it social tragedy for the patient's dependants and relatives, and that it is undoubtedly the most tragic of diseases, it will be realized that one cannot be too radical or too meticulous in combating it.

Argyll Robertson Pupil—From a series of observations in which the cat was employed as the experimental animal, Spiegel and Scala¹⁵⁰ con-

148 Sussman, M. L. Roentgen Examination of the Aorta and Pulmonary Artery, *Am J Roentgenol* **42** 75 (July) 1939.

149 Prendergast, F. G. General Paralysis of the Insane in Victoria, *M J Australia* **2** 361 (Sept 2) 1939.

150 Spiegel, E. A., and Scala, N. P. Role of the Cervical Sympathetic Nerve in the Light Reflex of the Pupil, *Arch Ophth* **23** 371 (Feb) 1940.

clude that the pathologic basis for the Argyll Robertson phenomenon should be sought in the reflex apparatus inducing contraction of the pupil and not in the dilator mechanism

Optic Atrophy—Moore and Woods¹⁵¹ present two papers reviewing the literature on syphilitic primary optic atrophy. The first considers the pathology and pathogenesis of the condition

This paper critically examines the recent literature on the pathology and pathogenesis of syphilitic primary optic atrophy. The scanty pathologic data available throw little light on the pathogenesis of the condition, although they seem conclusively to demonstrate that optic atrophy is not due to actual syphilitic inflammation of the optic nerves dependent on the presence therein of the causative organism

The newer theories as to the pathogenesis of optic atrophy are five

1 That it may be due to the virus of lymphogranuloma inguinale. This theory has so far nothing to support it

2 That it may be due to vascular constriction, functional or anatomic, within the optic nerves, with subsequent nutritional disturbances leading to atrophy, and that it may be relieved or arrested by the use of vasodilator drugs. This theory seems ill-founded, and is now largely abandoned

3 That it may be due to a disturbance of the inter-relationship between the factors of intraocular tension and retinal arterial systolic and diastolic blood pressure (the latter dependent on systemic hypotonia). This theory, advanced by Lauber and Sobanski, seems unsupported by the observed facts

4 That it may be due to adhesive optochiasmal arachnoiditis. While this theory may explain the occasional case, it certainly does not suffice for many others, in whom arachnoiditis cannot be demonstrated at operation or necropsy

5 That it may be due to the combination of neurosyphilis and nutritional deficiency. This theory has some clinical and more experimental backing, but requires much further study before it can be accepted

In short, it seems probable that the pathogenesis of syphilitic primary optic atrophy, so often (perhaps almost always) associated with tabes dorsalis, is identical with that of tabes dorsalis itself. This, in turn, is as yet unknown, though recent studies, especially in the field of nutrition, offer hope of its elucidation

The second paper deals with the results observed from treatment. The subject is so confused and standards of diagnosis, methods of treatment and the terms of post-treatment observation are so variable that again the authors find it impossible to draw definite conclusions. It appears to them, however, that subdural treatment and inoculation malaria are the methods which deserve further study and that triparamide is relatively contraindicated

¹⁵¹ Moore, J. E., and Woods, A. C. The Pathology and Pathogenesis of Syphilitic Primary Optic Atrophy. A Critical Review, *Am J Syph, Gonorr & Ven Dis* **24** 59 (Jan) 1940, Syphilitic Primary Optic Atrophy. II General Considerations and the Results of Treatment by Standard Methods (Especially Subdural Treatment and Induced Fever), a Critical Review, *Am J Ophth* **23** 145 (Feb) 1940

Neurogenic Bladder —Emmett¹⁵² calls attention to obstruction of the vesical neck, which undoubtedly frequently plays a large role in producing the tabetic bladder. According to his concept the presence of urinary retention should be regarded as an imbalance between the detrusor muscle and the vesicle neck. "Weakening" the vesical neck by surgical means should allow a weak detrusor muscle to empty the bladder. He reports 3 cases of *tabes dorsalis* in which the urinary difficulties were relieved by transurethral resection of prostatic tissue.

After four years Brodie, Helfert and Phifer¹⁵³ have restudied cystometrically 13 of a group of 24 patients with asymptomatic neurosyphilis. Only 3 of these 13 patients had normal cystometrograms when originally studied, and now only 2 have normal ones. The clinical diagnosis as to syphilis has been changed in 4 instances: from asymptomatic neurosyphilis to *tabes dorsalis* in 3 instances and to meningo-vascular neurosyphilis in 1. They conclude that neurologic changes can be demonstrated in the bladders of patients with asymptomatic neurosyphilis. These cystometric changes occur before symptoms referable to the bladder develop.

Myograms —From myographic studies on 20 patients, 7 of which are here reported, Kramer and Schaltenbrand¹⁵⁴ found spasticity and slight muscular rigidity in patients with dementia paralytica whether or not of the tabetic form, while hypotonia was the rule in patients with *tabes dorsalis*.

Charcot Joints —According to Sherwood and Hutchins¹⁵⁵ all observers are united in agreement with Volkmann's theory of multiple trauma made possible by virtue of loss of deep pain sense as the immediate cause of Charcot's joint, and not, as Charcot felt, some underlying trophic change in the joint. Their conclusions are based on the study of 15 cases, and 586 cases collected from the literature. They found that there were twice as many men as women, the condition occurred in all ages from 20 to 70, neurologic examination revealed some abnormality in 80 per cent, the ankle and foot were involved in 98 per cent, the knee in 60 per cent, the hip in 20 per cent, and the spine and upper extremities in 12 per cent, with involvement of more than one joint in 35 per cent of cases. In 60 per cent of cases the patients had positive reactions to serologic tests for syphilis. Disparity between the patient's

152 Emmett, J. L. "Tabetic Cord Bladder." *Newer Concepts in Diagnosis and Treatment*, Proc. Staff Meet., Mayo Clin. **15** 91 (Feb. 7) 1940.

153 Brodie, E. L., Helfert, I. H., and Phifer, I. A. "Cystometric Observations in Asymptomatic Neurosyphilis," *J. Urol.* **43** 496 (March) 1940.

154 Kramer, H., and Schaltenbrand, G. "Das Myogramm bei der *Tabes dorsalis* und bei der Paralyse," *Deutsche Ztschr. f. Nervenheilk.* **149** 117, 1939.

155 Sherwood, K. K., and Hutchins, L. R. "Charcot's Joints," *Northwest Med.* **38** 257 (July) 1939.

complaint and the physical findings is clinically the one factor more than any other to suggest the diagnosis. The onset may be insidious but usually is rather abrupt and is initiated either by a fall or by the spontaneous development of an acutely swollen, moderately painful joint. In either case, the swelling and pain become less acute in a short time, but residual weakness and unsteadiness occur and the typical flail joint develops.

Laboratory tests are of aid in making the diagnosis only if serologic reactions for syphilis are positive in blood and/or cerebrospinal fluid. The authors emphasize that these laboratory tests are a supplementary and not a diagnostic measure, typical Charcot joints may occur in patients whose tabes has "burned out" and who have negative serologic reactions both in blood and cerebrospinal fluid.

If made early enough, roentgenograms reveal changes consistent with ordinary but severe hypertrophic osteoarthritis. Later, however, the typical case reveals multiple, spontaneous, chip-type fractures with excessive capsular bony overgrowth and joint effusion.

Treatment should be based on the realization that the fundamental cause of the condition is multiple trauma to the joint. Reduction of this by fixation is essential and may be accomplished either by an external appliance or by arthrodesis. Antisyphilitic treatment as such is useless since the arthropathy is the result of previous damage to spinal cord pathways and is in itself neither a manifestation of progression of the neurologic lesion nor a lesion directly due to syphilis.

Batt and Hampton¹⁵⁶ were able to find 5 cases of spontaneous fracture of the neck of the femur through the site of the epiphyseal line occurring in adults. Three of the patients had tabes, a fourth had a positive reaction to serologic tests for syphilis in the blood but no signs of neurosyphilis. In the fifth patient the fracture was thought to be due to radiation osteonecrosis.

Hypertrophic Pachymeningitis—In the light of the fact that so few of the cases of hypertrophic spinal pachymeningitis which are found post mortem have been diagnosed clinically, Wilson, Bartle and Dean¹⁵⁷ attempt to correlate the more outstanding clinical features of the condition with the anatomic changes in 15 patients, 12 of whom came to necropsy.

The characteristic pathologic features are lymphocytic infiltration and fibrous hyperplasia of the dura which may be adherent to the piaarachnoid, compression of the spinal roots and secondary degeneration of the cord, particularly of the posterior columns and the dorsal and ventral spinocerebellar tracts. Chronic circu-

156 Batt, R. C., and Hampton, A. O. Spontaneous Subcapital Hip Fractures Occurring in Tabes Dorsalis, *J. Bone & Joint Surg.* **22** 137 (Jan.) 1940.

157 Wilson, G., Bartle, H., Jr., and Dean, J. S. Chronic Hypertrophic Spinal Pachymeningitis, *Am. J. M. Sc.* **198** 661 (Nov.) 1939.

latory insufficiency with resultant myelomalacia of the gray and white matter over several segments above and below the level of greatest involvement

Unfortunately, there are no pathognomonic features either of the symptomatology or the clinical manifestations. It is a disease of adults, is more common in men and is most frequently caused by syphilis (8 of the present 15), and the most usual symptom is root pain. Atrophy of the muscles with diminution or loss of reflexes at the level of the involved segments, with evidence of a lesion of the pyramidal tracts below, is the most common manifestation. There may be ataxia, difficulty in bladder function is not uncommon, and there frequently is an ill defined sensory level which may be of the dissociated type. Roentgenograms of the vertebral column show nothing unless there is associated Pott's disease or vertebral trauma, but studies after injection of iodized poppy-seed oil possibly offer the best method of verifying the diagnosis when it is suspected. Spinal manometry is of little help in excluding tumor of the cord, and negative results of the laboratory tests on the fluid are of no assistance.

When manometry has revealed a partial block, the authors feel that iodized oil is invaluable in differentiating pachymeningitis from tumor. They point out that "once the lipiodol passes a tumor there is an undelayed 'sheer drop' into the sacral cul-de-sac, but in pachymeningitis consecutive examinations over several days may reveal particles of oil suspended at varying regions below the clinical level." In addition, motor symptoms above the level of block argue against tumor, and a transient exacerbation of segmental symptoms after injection of iodized oil is in favor of the chronic inflammatory process.

In treatment, the authors recommend vigorous antisyphilitic therapy for these patients who have syphilis, pointing out, however, that this could hope to gain only arrest of further progress of the disease. For those without syphilis in whom tuberculosis as an etiologic agent can be excluded, they feel with most other authors that surgical decompression should be given more serious consideration.

Hassin and Zeitlin¹⁵⁸ present a case of cerebral hypertrophic pachymeningitis which serves particularly to point out the role which basilar pachymeningitis may play in causing bulbar paralysis.

Syphilitic Transverse Myelitis—Berman¹⁵⁹ notes that judging by the frequency of published reports acute syphilitic transverse myelitis, which formerly was a common manifestation of neurosyphilis, is becom-

158 Hassin, G. B., and Zeitlin, H. Syphilitic Cerebral Hypertrophic Pachymeningitis. Clinico-Pathologic Studies in a Case, *Arch Neurol & Psychiat* **43** 362 (Feb.) 1940.

159 Berman, S. Acute Syphilitic Transverse Myelitis. A Clinical Study and Report of a Case. *Arch Dermat & Syph* **41** 1078 (June) 1940.

ing rare In the past fifteen years only 5 cases have been reported in this country It is a disease of men with early syphilis who have had no or totally inadequate treatment and results from thrombosis of one of the spinal arteries, usually the anterior, in the dorsolumbar region of the cord The onset is commonly sudden, and signs and symptoms vary with the location and extent of the lesion Most often there are sudden, complete flaccid paralysis of both lower extremities and urinary retention, with constipation, sensory disturbances and trophic changes later developing Prodromal symptoms if present are not characteristic With the development of paralysis, the neurologic changes and the prognosis depend on the extent of injury to the various cord structures No characteristic changes in the cerebrospinal fluid occur, it may be quite normal

Pseudobulbar Palsy—Langworthy and Hesser¹⁶⁰ point out that pseudobulbar palsy is a syndrome about which little is known Even the term is a misnomer, supranuclear bulbar palsy would more accurately describe the lesion The cardinal clinical features of the condition are difficulties in speech, mastication and deglutition, without signs of injury to the bulbar nuclei In most instances it results from cerebral vascular lesions due to arteriosclerosis or syphilis

Syphilitic Polyneuritis—Simon and Berman¹⁶¹ describe the case of a patient with polyneuritis in which they attempt to indict syphilis as the etiologic agent, well realizing this to be difficult in view of the fact that the patient had had acute parotitis at the onset of the signs of neuritis and had previously had both bismuth and neoarsphenamine for the treatment of syphilis They say

The diagnosis of the syphilitic origin in this case must depend on the clinical history and examination, the positive serologic reactions of the blood and spinal fluid and the pathologic evidence that the clinical symptoms were due to pan-vasculitis, with infiltration in and about the walls of the blood vessels, associated with intimal proliferation, leading to obliterative endarteritis and endophlebitis This is a characteristic lesion of syphilis

Fetterman and Spitler¹⁶² list syphilis as a cause of peripheral neuritis This must be an extraordinarily rare condition

Treatment of Neurosyphilis—Merritt¹⁶³ expresses the belief that in the treatment of neurosyphilis the choice of a method for the adminis-

160 Langworthy, O R, and Hesser, F H Syndrome of Pseudobulbar Palsy. An Anatomic and Physiologic Analysis, Arch Int Med **65** 106 (Jan) 1940

161 Simon, A, and Berman, S Syphilitic Polyneuritis. A Clinicopathologic Entity, Arch Neurol & Psychiat **42** 273 (Aug) 1939

162 Fetterman, J L, and Spitler, D K Vascular Disorders of Peripheral Nerves, J A M A **114** 2275 (June 8) 1940

163 Merritt, H H Neurosyphilis and Its Treatment New England J Med **221** 817 (Nov 23) 1939

tration of fever depends much more on the facilities at hand than on any intrinsic differences in the value of inoculation malaria and fever induced by mechanical means

Binswanger¹⁶⁴ suggests the use of insulin in the control of lightning pains and reports unconvincing results in 1 patient

Black¹⁶⁵ and Macht¹⁶⁶ report more or less benefit in patients with tabes dorsalis to whom cobra venom was given to relieve lightning pains

Kroll¹⁶⁷ summarizes his study on the use of quartan malaria in the treatment of neurosyphilis

1 The literature of quartan fever in the therapy of neurosyphilis is reviewed

2 Sixty-two cases, all but 1 afflicted with one of the various forms of neurosyphilis, were inoculated intravenously. Seven, 5 of whom were colored, failed to show evidence of infection

3 The incubation period for white individuals averaged 143 days, and 191 days for negroes, the latter group exhibiting the greater number of variations. The so-called latent incubation period may extend as much as three to four months

4 The average height of paroxysms ranged from 104.5 to 106° F

5 A relatively small number of complications were met with and they were easily and successfully handled

6 One patient (18 per cent) died as result of quartan malaria

7 Malarial relapses, which occurred in 8 per cent of patients, may be definitely avoided by the use of atabrin and plasmochin in combination with quinine

8 Response of the blood Wassermann reaction was poor even after prolonged observation and postmalarial treatment

9 Of the 23 general paretics who could be followed, 3 died, 1 as the result of malaria and the other 2 of causes unrelated to neurosyphilis, 4 gained no improvement, 1 manifested moderate improvement, 10 showed incomplete remission, and 5 regained complete former levels

10 Eleven patients with asymptomatic neurosyphilis exhibited no progression, all but a few showed varying degrees of improvement in the spinal fluid

11 Of the 13 tabetics, 1 died of a cause unrelated to neurosyphilis, all showed varying grades of relief. In 5 out of the 6 cases with primary optic atrophy, conservation of existing sight was achieved

12 Improvement was noted in all 5 with meningovascular neurosyphilis

13 A large number of patients had a considerable amount of pre- and postmalarial therapy which partially obscured the effects of quartan malaria

164 Binswanger, H. Kasuistischer Beitrag zur Bekämpfung tabischer Krisen. Insulin zur Stillung lanzinierender Schmerzen, Schweiz med Wchnschr **69** 1327 (Dec 30) 1939

165 Black, N. T., Jr. Cobra Venom for the Relief of Pain, South M J **33** 432 (April) 1940

166 Macht, D. I. Cobra Venom Therapy in Dermatology and Syphilology, Urol & Cutan Rev **44** 119 (Feb) 1940

167 Kroll, M. M. Quartan Malaria in the Treatment of Neurosyphilis, Am J Syph, Gonorr & Ven Dis **24** 148 (March) 1940

14 The complement fixation reaction of the cerebrospinal fluid showed the least response following quartan malaria. The cell count and protein content were more readily influenced. Mastic curve changes were observed to parallel the protein variation.

15 No direct correlation was found between clinical and serologic improvement.

Fong¹⁶⁸ analyzes the results of inoculating 436 Negro patients with neurosyphilis with quartan malaria. This was successful in only 229 or 53.2 per cent, and failure was more common among those patients with the more negroid features. Six, or 2.5 per cent, of the successfully inoculated patients died as a direct result, and among the remainder 13.9 per cent were greatly improved by treatment, 33.1 per cent were improved and 52.8 per cent were unimproved.

Kopp and Solomon¹⁶⁹ analyzed the records of 302 patients with neurosyphilis who had been treated with malaria in an effort to determine whether the height and duration of the produced fever could be related to the therapeutic results. They find the best results to obtain in those patients who had more than one hundred and fifty hours of fever with a temperature above 100 F, but could observe no correlation between the height of the peaks and the eventual outcome. By corollary, patients who had more than ten paroxysms were improved more often than those who had less.

From their experience with the treatment of 155 patients with dementia paralytica by means of inoculation malaria, Mays, Oden and Cox¹⁷⁰ comment:

Our limited experience with the two types of malaria would seem to indicate that quartan malaria is preferable to tertian malaria in the treatment of dementia paralytica because of its higher improvement rate, its lower death rate and the more prolonged temperature elevation.

The grandiose-excited type carries the most favorable and the simple deteriorated type the least favorable outlook for recovery.

A minimum of 15 paroxysms with temperature elevations of 104 degrees or above is desirable. The severity of the paroxysms, rather than the number, is the therapeutic desideratum.

It is frequently advisable to precede malaria therapy with a course of tryparsamide and thio-bismol in very debilitated patients.

168 Fong, T. C. C. Therapeutic Quartan Malaria in the Therapy of Neurosyphilis Among Negroes, *Am J Syph, Gonorr & Ven Dis* **24** 133 (March) 1940.

169 Kopp, I., and Solomon, H. C. The Malarial Treatment of General Paresis. Relation of the Height, Duration, and Frequency of Fever to the Clinical and Serologic Results, *Am J Syph, Gonorr & Ven Dis* **23** 585 (Sept.) 1939.

170 Mays, J. R. S., Oden, J. W., and Cox, C. G. Malaria Therapy in Dementia Paralytica. A Statistical and Sociological Study of Three Hundred Cases Treated with Tertian or Quartan Malaria and Tryparsamide Over a Seven-Year Period, *South M J* **33** 255 (March) 1940.

The death rate can be materially lowered by careful observation and proper symptomatic treatment of the patient during the acute and postmalaria period. During the febrile periods the patient should receive fruit juices and sodium chloride. Anemia and cachexia will improve with tube feeding, ferrous sulphate administration and repeated small whole blood transfusions.

Psychotic symptoms such as hallucinations, grandiose or paranoid delusions and hypochondria frequently show an exacerbation during the period of acute malaria, but clear up readily with the administration of quinine and are of no consistent prognostic significance.

Convulsions appearing in cases of dementia paralytica tend to decrease the recovery rate and to increase the mortality rate. The number and severity of convulsive seizures tend to decrease following malaria therapy, although the reverse is frequently true during the period of active malaria.

We were unable to establish an absolute correlation between the clinical and serologic improvement.

There was no significant improvement in the neurologic symptoms following malaria therapy.

Bennett, Nielsen, Fechner and Cash¹⁷¹ report on the treatment of neurosyphilis with combined fever and chemotherapy.

Untoward Effects from Fever Therapy—Neymann and Osborne¹⁷² say

1 The main dangers of artificial fever produced by physical means are exhaustion, burns and death.

2 Death as a result of electropyrexia is a rare occurrence and can be avoided by good clinical judgment and proper care.

3 Heat stroke can and must be avoided. Patients must never be allowed to reach a temperature above 42.5° C (108.5° F). Under ordinary conditions a maximum temperature of 41.5° C (106.7° F) suffices for all clinical needs. Pyrometers are valuable for reading a patient's temperature from moment to moment.

4 External heating is more exhausting than penetrating heat. It reverses the natural thermal gradients of the body by heating the skin higher than the viscera. It also deprives the body of its physiological safety valves by heating the extremities to the same degree as the torso. It relatively increases the heart rate and decreases the sweat production.

5 Adding moisture to the air of a hot air cabinet makes the heating of the patient more efficient but does not alter the unphysiological action of external heat. The much applauded and so-called intrinsic value of air-conditioning alone is therefore a myth.

6 Burns can be avoided by proper technic. Conventional spark gap diathermy machines are inclined to cause a liquefaction of the subcutaneous fat and should not be used for producing fever in very obese individuals. No machines are fool proof. All may cause burns if improperly used. This applies to electric blankets,

171 Bennett, A. E., Nielsen, J. C., Fechner, A. H., and Cash, P. T. Combined Artificial Fever and Chemotherapy in Dementia Paralytica. Preliminary Report of Seventy Cases, *Arch. Phys. Therapy* **20**: 620 (Oct.) 1939.

172 Neymann, C. A., and Osborne, S. L. The Dangers of Electropyrexia, *M. Rec.* **150**: 423 (Dec. 20) 1939.

diathermy machines, radiotherms, hot air cabinets with or without air-conditioning and inductotherms

7 It is important to attempt to replace the sodium chloride lost through perspiration by having the patient drink six-tenths percent sodium chloride solution during treatment. The tendency towards acidosis may be influenced by giving fruit juices and sugar solutions.

Wilson¹⁷³ reports briefly on the clinical and autopsy observations on 4 patients who died of heat stroke, 1 from the sun and 3 from induced artificial fever. Gross hyperpyrexia was the most striking clinical feature, and the pathologic change common to all 4 cases and probably the actual cause of death was extensive hemorrhage under the endocardium of the left ventricle, especially on the septal wall in the region of the bundle of His.

Treatment of Malaria Inoculata—Grimm¹⁷⁴ brings out the fact that in the termination of inoculation malaria it is necessary to utilize full doses of potent antimalarial drugs over appropriate periods of time in order to prevent relapse. Young and McLendon¹⁷⁵ show that both mapharsen and tryparsamide relieve symptoms of induced quartan malaria without eradicating the infection.

SYPHILIS AND PREGNANCY

"*Syphilis in Mother and Child*" is the title of a brochure by Cole, Jeans and collaborators¹⁷⁶ which was published as a supplement to *Veneral Disease Information* and so is available for widespread distribution. It provides a summary of current consensus on the problems implied in the title but is weakest in the most troublesome field, i.e., the management of an apparently normal child born to a mother with syphilis.

By a modification of the questionnaire method, Fluent¹⁷⁷ sought to determine why pregnant women do not avail themselves of antepartum care as early as is necessary for the health and safety of mother and baby. The most common reason could be classified under "inability to recognize need for medical care."

173 Wilson, G. The Cardiopathology of Heatstroke, *J A M A* **114** 557 (Feb 17) 1940

174 Grimm, K. Beitrag zur Therapieresistenz der Impfmalaria, *Dermat Wchnschr* **110** 179 (March 2) 1940

175 Young, M. D., and McLendon, S. B. Treatment of Induced Malaria in Negro Paretics with Mapharsen and Tryparsamide, *Pub Health Rep* **54** 1509 (Aug 18) 1939

176 Cole, H. N., Jeans, P. C., and others. Syphilis in Mother and Child, *Ven Dis Inform*, 1940, supp 7, p 1

177 Fluent, M. A. Securing Early Antepartum Care, *Pub Health Nursing* **32** 28 (Jan) 1940

Syphilis as a Cause of Fetal and Neonatal Deaths—Adair and Potter¹⁷⁸ found that 371 neonatal deaths and 402 stillbirths had occurred in the course of the delivery of 17,728 patients. Syphilis was a minor factor as a cause of death in this group. Thirteen of the mothers gave positive reactions to serologic tests for syphilis, but only 4 infants were thought to have died as a result of syphilitic infection.

During a period in which their agency had supervised 16,834 deliveries, mostly in patients' homes, Buxbaum and Udesky¹⁷⁹ were able to find 128 cases (0.7 per cent) in which intrauterine death of the fetus was known to have taken place after the twenty-eighth week and before the onset of labor.

Increasing age, a history of repeated abortions or stillbirths and larger number of previous pregnancies obviously made for an increased tendency to develop this complication. Syphilis and late toxemias of pregnancy were the most important associated diseases.

Effect of Treatment—Halloran¹⁸⁰ seized the opportunity to determine the effects of varying amounts of antisymphilitic treatment on the expectant mother by following the outcome for the product of conception in 513 women with syphilis. Sixteen women had received no antisymphilitic treatment, 2 of these delivered stillborn infants, and 11 gave birth to living children with syphilis. Only 3 infants of these mothers were apparently nonsymphilitic. Among the 264 women who received less than six intravenous injections of an arsenical drug, the pregnancies in 20 terminated in abortion or stillbirth, in 53 resulted in syphilitic infants and in 191 (72 per cent) resulted in living, apparently nonsymphilitic infants. Similarly, among the 149 women who received from six to ten intravenous treatments 119 (80 per cent) produced living children who apparently were well. Even more striking was the fact that among the 84 women who received more than ten intravenous injections with accompanying heavy metal there were no abortions or stillbirths and only 6 of their children had syphilis.

Astrachan's¹⁸¹ data on the outcome of pregnancy for women with syphilis emphasize that regardless of treatment the risk to the fetus is greater the more recent the infection of the mother.

178 Adair, F. L., and Potter, E. L. Fetal and Neonatal Disease and Death, *Am J Obst & Gynec* **37** 993 (June) 1939.

179 Buxbaum, H., and Udesky, I. C. Intrauterine Death of the Foetus After the Twenty-Eighth Week, *Am J Obst & Gynec* **39** 659 (April) 1940.

180 Halloran, C. R. A Review of the Records of Syphilitic Pregnant Women Treated at the Los Angeles Maternity Service Over a Ten-Year Period, *Am J Obst & Gynec* **38**, 135 (July) 1939.

181 Astrachan, G. D. Syphilis in Pregnancy, *New York State J Med* **40** 43 (Jan 1) 1940.

CONGENITAL SYPHILIS

Incidence—According to Talbot,¹⁸² there has been a 50 per cent reduction in the reported cases of early congenital syphilis in Connecticut during the three and a half years the premarital blood test law has been in effect in that state

Clifton and Heinz⁴⁶ found 26, or 0.46 per cent, of 5,625 children admitted to a large children's hospital to have congenital syphilis. Negro children constituted only 3.3 per cent of all children but formed 18 per cent of those with congenital syphilis.

Kemkes¹⁸³ found that among 6,337 average public school children in Frankfort on the Main 14 (0.22 per cent) had congenital syphilis. The same was true of 8 among the 745 retarded school children and of 2 among the 201 children in the deaf and dumb institute, but of none of the 349 intermediate school children.

Hereditary Ectodermal Dysplasia—De Silva¹⁸⁴ reviews the literature on hereditary ectodermal dysplasia of the anhydrotic type, reports 4 personally observed cases and brings out the differential diagnostic points between this condition and congenital syphilis. The teeth are malformed but easily may be distinguished from Hutchinson's teeth. Fissuring to be confused with rhagades is sometimes present but is usually about the nose rather than the mouth. Corneal opacities are sometimes present. Hypotrichosis and absence of sweat glands are common.

Clavicular Sign—The significance of enlargement of the medial end of the clavicle (Higoumenakis' sign) as a diagnostic sign of congenital syphilis has not been settled. Young¹⁸⁵ found 6 consecutive patients with late congenital syphilis to have definite enlargement of the medial end of the clavicle. Dax and Stewart,¹⁸⁶ however, examined 64 congenitally syphilitic patients (29 female and 35 male) for the sign and found it in only 19 (29.7 per cent). It was also present in 65 (5.4 per cent) of 1,200 patients, half of them male, examined as controls.

Changes Observed Roentgenologically in Bones—In an effort to clarify some of the difficulties involved in making the diagnosis of con-

182 Talbot, H. P. Premarital Blood Tests and Congenital Syphilis, Connecticut Health Bull. **1** 229 (Sept.) 1939

183 Kemkes, B. Zur Frage der Häufigkeit der Lues Congenita, Ztschr. f. Kinderh. **61** 121 (June) 1939

184 de Silva, P. C. C. Hereditary Ectodermal Dysplasia of the Anhydrotic Type, Quart. J. Med. **8** 97 (April) 1939

185 Young, K. L. Clavicle Sign of Late Congenital Syphilis, Arch. Dermat. & Syph. **41** 1060 (June) 1940

186 Dax, E. C., and Stewart, R. M. The Sign of the Clavicle, Brit. M. J. **1** 771 (April 15) 1939

genital syphilis during the first few months of life, Christie¹⁸⁷ studied 83 infants born of syphilitic mothers by roentgenographic examination of the long bones. By this means a diagnosis of syphilis, later shown by clinical and serologic follow-up to be correct, was made early in only 2 instances. The diagnosis of "no syphilis" was made on the basis of roentgenographic examination in 47 instances, and this was later shown by follow-up to be correct. In 23 instances the roentgenologic diagnosis was reported as doubtful, the mothers of 22 of these 23 infants had been treated with bismuth during the pregnancy. He concludes

Since conditions other than syphilis may bring about changes in the bones apparent in roentgenograms, it is advisable to confirm the roentgenographic findings by clinical or serologic examinations before a definite diagnosis of syphilis is made and treatment for the disease is instituted.

Caffey¹⁸⁸ has made an extensive study of roentgenography of infants' bones, with particular reference to the usefulness of the method in the early diagnosis of congenital syphilis. He summarizes the present contribution as follows:

Roentgenograms of the skeletons of 550 non-syphilitic infants were studied. The significant clinical and laboratory data with roentgenograms from 22 selected cases are presented.

These roentgenograms show changes indistinguishable from syphilitic osteochondritis, syphilitic osteoperiostitis and syphilitic osteomyelitis.

The earliest and most frequent forms of syphilitic osteochondritis were simulated in 14 patients with bacteremia (due to staphylococcus, pneumococcus and tubercle bacillus), erythroblastosis foetalis, septic hemolytic anemia, familial hemolytic anemia, multiple birth injuries, congenital atresia of the biliary apparatus, severe malnutrition, unexplained hemiparesis, protozoan encephalitis and maternal bismuth therapy. In this non-syphilitic group no cases resembling the following rarer types of syphilitic osteochondritis were found, (1) "saw-tooth" metaphyses, (2) foci of rarefaction in the angles of the cartilage-shaft junctions, (3) multiple infarctions through the ends of the shafts.

Both diffuse syphilitic osteoperiostitis and syphilitic osteoperiostitis callosa were simulated in healing rickets, prematurity, traumatic periostitis of the newborn, gonococcal bacteremia and undiagnosed disorders of nutrition.

Syphilitic osteomyelitis was simulated in multiple pyogenic osteomyelitis. Wimberger's sign, symmetrical osteomyelitis of the proximal medial aspects of the tibiae, was not encountered in this nonsyphilitic group.

The roentgenographic skeletal lesions of early infantile syphilis are simulated in a wide variety of conditions in young infants.

187 Christie, A. U. The Value of Roentgenographic Examination in the Diagnosis of Syphilis in Newborn Infants, *J. Pediat.* **15** 230 (Aug.) 1939.

188 Caffey, J. Syphilis of the Skeleton in Early Infancy. The Nonspecificity of Many of the Roentgenographic Changes, *Am. J. Roentgenol.* **42** 637 (Nov.) 1939.

The roentgenographic findings in the skeleton *per se* are not conclusively diagnostic of early infantile syphilis and they should not be used *alone* as presumptive evidence for the institution of antisyphilitic therapy

Osteochondritis, osteoperiostitis and osteomyelitis present in combinations are more indicative of syphilis than the presence of any of these lesions alone

In evaluating roentgenographic bone changes in young infants we would do well to remember the advice of Wimberger and of McLean

Wimberger "If in a case there are no other conclusive factors which make possible the diagnosis of syphilis, the roentgen findings as a rule will not make the diagnosis"

McLean "Roentgenographic examination is not intended to offer the clinician a substitute for scrupulous clinical examination nor is it suggested that roentgenology will ever assume the place now held by serology in the diagnosis of the disease It is only by the correlation of clinical, serologic and roentgenologic observations that the knowledge of congenital syphilis will be furthered"

The same author^{1c} describes changes in the long bones of infants newborn to syphilitic mothers who had been treated with bismuth during pregnancy, he believed these changes to be due to deposition of bismuth but felt that syphilitic osteochondritis could not be excluded The distinction is so important that in an effort to gain further information Whitridge¹⁸⁹ gave intramuscular injections of a bismuth compound to 12 nonsyphilitic women during the last trimester of pregnancy Roentgenograms of the long bones of their children made during the first week of life showed areas of increased density, similar to those observed by Caffey, in 9, no change in 2 and questionable changes in 1 One infant died on the second day of life, after a difficult breech delivery

Microscopic sections of the upper end of the tibia, the lower end of the femur and a rib were studied The histologic changes were the same in each The mature cartilage cells were arranged in an orderly fashion and there was no increase in the width of the zone of fully grown cartilage At the cartilage shaft junction the invasion of cartilage cell columns was entirely normal in appearance However, there was an excessive amount of calcified matrix substance and this extended down into the shaft as a dense zone for about 1 mm The presence of this excessive matrix seemed to be due to an excessive deposition as well as failure in destruction These trabeculae of calcified matrix were for the most part devoid of bone, although there were numerous osteoblasts surrounding each As one progressed further into the shaft, this darkly staining matrix began to be encased in bone so that approximately 2 mm below the cartilage shaft junction there was a zone of dense bony trabeculae laid down upon a scaffold of calcified matrix substance Still further down the shaft the trabeculae were thinner, much less dense and resembled the structure of normal bone There was no excess of osteoclasts such as is seen in lead poisoning The marrow elements were entirely normal

189 Whitridge, J, Jr Changes in the Long Bones of Newborn Infants Following the Administration of Bismuth During Pregnancy, Am J Syph, Gonorr. & Ven Dis 24 223 (March) 1940

Interstitial Keratitis —(a) Pathogenesis In a contribution which is potentially of major importance, Kruse¹⁹⁰ and his collaborators present observations of the ocular changes observed in a small group of patients known to be receiving insufficient riboflavin and describe improvement in these lesions which took place when adequate riboflavin was added to the diet. Since morphologically the lesion in the cornea resembled that seen in interstitial keratitis in patients with congenital syphilis, the authors sought patients with that condition to treat. They report the cases of 2 patients, a child 9 years of age with congenital syphilis and a woman 24 years old with acquired syphilis, who suffered from progressive interstitial keratitis in spite of regular antisyphilitic treatment. Two patients to serve as control were given tablets of acetylsalicylic acid, the 2 experimental patients were given riboflavin, and all antisyphilitic medication was stopped. The authors relate that remarkable improvement occurred in the inflammatory process in the eyes of the treated patients. They are not convincing.

They promise further observations and later a detailed comparative study of the morphology of the changes in the cornea in ariboflavinosis and in various forms of keratitis.

A contrasting observation of great interest is provided by Dean, Dean and McCutchan¹⁹¹. These authors describe the cases of 6 patients with interstitial keratitis who were relieved by the identification and removal of an offending food or foods by an elimination diet, only to have the process recur if the food was taken again.

Klauder's¹⁹² discussion of the various theories as to the pathogenesis of interstitial keratitis and his fruitless attempts to confirm any of them experimentally again emphasizes the necessity for extreme caution in associating this condition with any one pathogenic mechanism until a clearer classification of interstitial keratitis into its various forms is available.

(b) Clinical Manifestations Klauder and Cowan¹⁹³ stress the fact that almost without exception some residual of an attack of interstitial keratitis remains. Often these corneal scars can be seen by ordinary

190 Kruse, H. D., Sydenstricker, V. P., Sebrell, W. N., and Ceckley, H. M. Ocular Manifestations of Ariboflavinosis, *Pub Health Rep* **55** 157 (Jan 26) 1940.

191 Dean, A. M., Dean, F. W., and McCutchan, G. R. Interstitial Keratitis Caused by Specific Sensitivity to Ingested Foods, *Arch Ophth* **23** 48 (Jan) 1940.

192 Klauder, J. V. Clinical and Experimental Study of Interstitial Keratitis, *J Invest Dermat* **2** 157 (Aug) 1939.

193 Klauder, J. V., and Cowan, A. Corneal Examination and Slit Lamp Microscopy in the Diagnosis of Late Congenital Syphilis, Especially in Adults, *J A M A* **113** 1624 (Oct 28) 1939.

examination, but at times they are so small that they cannot be detected except by slit lamp microscopy

Kopp and Solomon¹⁹⁴ bring out the infrequent association of untreated juvenile dementia paralytica and interstitial keratitis but report several instances of the appearance of the ocular lesion in juvenile patients with dementia paralytica who had been given fever therapy. They draw the obvious analogy between this phenomenon and the often reported occurrence of gummatous lesions after malarial treatment of acquired dementia paralytica and relate it to an alteration in the patient's immune status produced by artificial fever.

Treatment—Heymann and Enright¹⁹⁵ feel that children with interstitial keratitis who do not show improvement from routine treatment should be given the benefit of two weeks of daily artificial fever therapy.

Physical and Mental Growth in Juvenile Dementia Paralytica—The Harvard Graduate School of Education¹⁹⁶ has sponsored a nonmedical physical and psychologic study of children entering the first grade in school in selected communities. Yearly measurements of these children were made, and later admissions to mental disease hospitals in the localities were surveyed to discover children among those measured in whom a psychosis had developed. One patient had been hospitalized for the juvenile form of dementia paralytica at 15 years of age. Growth and mental records were available for the six years prior to his admission to the hospital. He had been normal in mental and physical growth at the eighth and ninth year levels but showed retardation in physical and intellectual development at 10 years of age. During the three years prior to admission there was no physical growth, and learning capacity fell to the level of an imbecile.

Treatment—Howles¹⁹⁷ presents a detailed analysis of his experiences in the treatment of congenital syphilis. The scheme in use in his clinic calls for the intramuscular injection of sulfarsphenamine, alternating withunctions of mercury for children less than 1 year of age and

194 Kopp, I, and Solomon, H. C. Interstitial Keratitis in Patients with Neurosyphilis of Congenital Origin, with a Discussion of Fever as a Precipitating Factor of Keratitis in the Paretic Variety, *Am J Syph, Gonorr & Ven Dis* **23** 751 (Nov.) 1939

195 Heymann, W., and Enright, L. S. Artificial Fever Treatment in Infants and Children. Methods, Indications and Results, *Ohio State M J* **36** 40 (Jan.) 1940

196 Gardner, G. E. Prepsychotic Measurements of Physical and Mental Growth in a Case of Juvenile Dementia Paralytica, *Arch Neurol & Psychiat.* **42** 121 (July) 1939

197 Howles, J. K. The Treatment of Congenital Syphilis with an Intravenous Arsenical. An Analysis of Two Hundred and Four Clinical Cases, *South M J* **32** 940 (Sept.) 1939

intravenous injections of mapharsen, alternating with intramuscular injections of a suspension of bismuth subsalicylate in oil, for those older. Forty-six children received the former treatment, and 204 children received mapharsen. This was administered alone to 59 and was combined with bismuth subsalicylate for 145. From the immediate results which he observed Howles concludes:

The good results which follow the intravenous use of "mapharsen" in prenatal and congenital syphilis would seem to merit its acceptance as a standard mode of therapy in such cases. The addition of bismuth subsalicylate to the "mapharsen" therapy produces even more satisfactory results.

Lyon and O'Neil¹⁹⁸ compare the results achieved by treating a group of congenitally syphilitic children with acetarsone and a group with other arsenical compounds. In both groups the children received heavy metal in alternation. All were adequately treated according to arbitrary standards. The authors observed no significant differences between the average outcome for the two sets of drugs, but were impressed with the fact that regardless of the drug used, children who came under treatment before 2 years of age did better than those older.

In reviewing their experience in five children's venereal disease clinics which are under their control, Lyon and Seymour¹⁹⁹ were struck by three factors: (a) the inadequacy of antepartum treatment in syphilitic pregnant women, (b) failure of parents to cooperate in the treatment of their children with syphilis, and (c) delay in instituting treatment in children with syphilis after the disease was, or might have been, diagnosed. They are so disturbed about this situation that they recommend the routine administration of acetarsone to every child born of a mother with inadequately treated syphilis. This procedure obviously begs the question. The control of congenital syphilis depends on (a) prevention, by the early recognition and proper treatment of syphilis in the pregnant woman, (b) early diagnosis of the disease in the infant born of a woman with syphilis, and (c) proper treatment of the infant with congenital syphilis as soon as the diagnosis is established.

All three of these depend on cooperation of the expectant or actual parent; lacking that, it would seem highly unwise to attempt to devise a method of treatment which is a substitute for one that failed because of lack of cooperation on the part of the mother, but which itself depends on another form of understanding cooperation that is probably more difficult to achieve.

198 Lyon, R. A., and O'Neil, F. C. Congenital Syphilis. Comparison of Treatment with Acetarsone and Other Arsenicals, *J. Pediat.* **15** 19 (July) 1939.

199 Lyon, R. A., and Seymour, M. Congenital Syphilis. I. Routine Treatment with Acetarsone of Infants Whose Mothers Were Inadequately Treated During Pregnancy, *J. Pediat.* **15** 13 (July) 1939.

Givan and Villa²⁰⁰ used trisodarsen (trisodium salt of 3,3'-diamino-4,4'-dihydroxyarsenobenzene-N,N'-dimethylene sulfonic acid) in the treatment of 147 patients with congenital syphilis. There were no deaths. The remainder of their report is of dubious value, since they speak of "curing" interstitial keratitis and imply that nerve deafness improved.

Keratoplasty—Castroviejo,²⁰¹ McKinney²⁰² and Kirwan²⁰³ call attention to corneal transplants as a method of restoring vision to an eye rendered useless by corneal opacities. The great difficulty is in obtaining suitable donor material, collaboration between ophthalmologists, with every enucleated eye made available for donor purposes, is suggested.

SYPHILIS AND OTHER DISEASES

Tuberculosis—Among 2,160 patients admitted to a tuberculosis sanatorium, Warring²⁰⁴ discovered that there were 87, or 4 per cent, for whom a definite diagnosis of syphilis could be made. When this percentage was broken down according to race, 32 per cent of the white patients and 26 per cent of the colored patients had both tuberculosis and syphilis. In addition, there were 22 patients for whom one or more doubtful or positive serologic tests were obtained who were finally decided to be nonsyphilitic. In 11 of these there had been a single unverified or unrepeatable doubtful or positive reaction, but in the other 11 repeated doubtful reactions had been obtained. The author relates these to the possible effect of tuberculous toxemia in producing false doubtful or false positive serologic reactions for syphilis, a suggestion which has recently been made by Parran and Emerson.^{1e}

None of the patients had early syphilis, in 68 of the 87 this disease was latent, and the remainder exhibited various late manifestations save 4 who were apparently cured. From a study of the literature Warring concludes that there is no evidence to indicate that the development of active tuberculosis occurs more frequently in patients with syphilis than among those who are nonsyphilitic, nor in his material was there evidence to indicate an increase in the extent of the tuberculous infection in those patients with syphilis. In analyzing the course of the tuberculous infection under treatment, however, he found that those patients with both

200 Givan, T. B., and Villa, G. Trisodium Arsphenamine Sulfonate (Trisodarsen) in the Treatment of One Hundred and Forty-Seven Cases, *Am J Syph, Gonorr & Ven Dis* **23** 771 (Nov.) 1939.

201 Castroviejo, R. Present Status of Keratoplasty, *Arch Ophth* **22** 114 (July) 1939.

202 McKinney, J. W. Transplantation of the Cornea, *South M J* **33** 205 (Feb.) 1940.

203 Kirwan, E. O. Transplantation of the Cornea. Report of a Perfect Case, *Arch Ophth* **22** 21 (July) 1939.

204 Warring, F. C., Jr. Coexisting Tuberculosis and Syphilis, *Am Rev Tuberc* **40** 175 (Aug.) 1939.

syphilis and tuberculosis in general did less well than those with tuberculosis alone. Not all of the patients had antisyphilitic treatment, but no effort is made to evaluate the additional factor of treatment in those who did. Contrariwise, the course of the syphilitic infection in patients with tuberculosis did not seem to be materially different from the course of the disease in the nontuberculous.

Regarding the indications for the treatment of syphilis in patients with tuberculosis, Warring says

(1) If the syphilitic disease is in an infectious stage, treat it to the point of noninfectivity, no matter what the extent or type the tuberculosis. (2) Should the syphilis be of the latent stage, attention should be paid first to the age of the patient. Patients over sixty can usually be safely allowed to forego antisyphilitic treatment. If the patient is younger, evaluate the pulmonary disease. Do not treat patients with far advanced, progressing tuberculosis who appear to have a hopeless prognosis. If the far advanced disease later shows definite evidence of improvement, antisyphilitic treatment can then be started cautiously. Delay treatment in patients with acute, active or exudative types of tuberculosis, no matter how small the extent of the tuberculosis. Treat patients with previously active pulmonary disease as soon as it becomes quiescent. (3) In patients with certain early manifestations of active late syphilis (aortitis, aneurysm, central nervous system syphilis) treat the syphilis if it is felt that the patient's life may sooner be endangered by syphilitic infection than by his chronic pulmonary tuberculosis. Whereas treatment of syphilis can be delayed in the latent syphilitics while the progress of the tuberculosis is observed, it should be begun at the earliest possible moment in patients with active late syphilis. (4) Suspend treatment of syphilis if the patient has febrile reactions, haemoptyses, develops wet pleurisy or shows by X-ray spread of tuberculosis.

According to these principles 35 of the 87 patients with both syphilis and tuberculosis were given antisyphilitic treatment. It is not possible to draw very broad conclusions from so small a group, but the response of the syphilitic infection to treatment in tuberculous patients appeared not to differ from that expected in the nontuberculous. The author feels that the question of the influence of antisyphilitic treatment on the course of tuberculosis cannot be answered.

Trail²⁰⁵ feels that long-standing or well treated syphilitic infection facilitates the production of a more fibrous type of tuberculous lesion.

Semon²⁰⁶ calls to attention the rarity of the primary lesion of tuberculosis in an externally visible area and discusses the differential diagnosis of such lesions from primary lesions of syphilis.

Nephritis—With the report of 2 cases, Baker²⁰⁷ reviews in some detail the confusing subject of the relationship of syphilis and nephritis.

205 Trail, R. R. Pulmonary Tuberculosis and Syphilis, *Brit J Ven Dis* **15** 171 (July) 1939.

206 Semon, H. C. G. Tuberculosis and Syphilis, *Brit J Ven Dis* **15** 159 (July) 1939.

207 Baker, B. M., Jr. The Relation of Syphilis to Nephritis, *Bull Johns Hopkins Hosp* **65** 196 (Aug.) 1939.

As he points out, diagnostic accuracy is essential, because if the nephritis is due to syphilis vigorous treatment is indicated, but its presence as a coincidental disease may make modifications in antisyphilitic treatment necessary

He would identify three types of nephritis due or related to syphilis

1 Hemorrhagic nephritis indistinguishable from more usual forms of the same condition and actually probably due to the usual (streptococcal) organism, whose entry into the body has been facilitated by the pharyngeal lesions of early acquired or congenital syphilis

2 Lipoid nephrosis entirely similar to other forms of lipoid nephrosis but with a dramatic response to antisyphilitic treatment

3 The syphilitic nephritis of Rich, which is a pathologic entity and rarely, if ever, becomes clinically manifest

Book Reviews

Proctoscopic Examination and Diagnosis and Treatment of Diarrheas
By M H Streicher, M D, Assistant Professor of Medicine, University of Illinois Price, \$3 00 Pp 149, with 39 figures and 3 tables Springfield, Ill, and Baltimore Charles C Thomas, 1939

This volume deserves favorable recognition It is a well dressed book, almost a primer, small enough to fit readily into one's pocket, well printed and clearly illustrated There is a bibliography of fifty-eight references which evidently have been selected as worthy representatives of sound proctology There is an adequate index

The contents are divided into seven parts In the first part the technical side of proctologic examination is well explained Then the common causes of diarrhea and their methods of treatment are considered The author argues that for practical purposes in clinical work six fundamentally different kinds of diarrhea should be recognized These are as follows diarrheas of mechanical origin, usually from tumors and occasionally from adhesions, diarrheas from impaired digestive secretion, diarrheas from abnormal metabolism, diarrheas from drugs or of nervous origin, infectious diarrheas, diarrheas secondary to general disorders such as nephritis or leukemia, and finally, diarrheas due to abnormal anatomy such as those complicating an enterocolic or rectovaginal fistula Such a classification of diarrheas is arbitrary but nevertheless of undoubted usefulness The methods of treatment advocated for these various diarrheas are sensible Due emphasis is placed repeatedly on the essential need of accurate diagnosis

On the whole, the book is workman-like Practitioners and students should enjoy it

Diagnostic Signs, Reflexes and Syndromes By Wm Egbert Robertson, M D, Visiting Physician, Philadelphia General Hospital, and Harold F Robertson, M D, Instructor in Medicine, University of Pennsylvania Price, \$3 50 Pp 309 Philadelphia F A Davis Company, 1939

This is a queer book and of an entirely new type, as is stated in the publisher's foreword It is no less than it pretends to be, a compendium of physical signs, reflexes and syndromes

In a painstaking manner and overlooking or forgetting very few, the authors have collected and tabulated the physical signs, reflexes and syndromes with which any observer's name has ever been related, and these they have set down in alphabetical order A great many names appear which the usual clinician does not associate with the physical signs described, and a great many signs are named which do not appear of especial importance The book on the whole, however, is worth owning for reference work if one is interested in the use of a novel form of medical dictionary

Do You Want to Become a Doctor? By Morris Fishbein, M D, Editor, Journal of the American Medical Association Price, \$1 50 Pp 176 New York Frederick A Stokes Company, 1939

Prospective medical students eager to learn something of the lure of medicine frequently ask what the study of medicine is all about, what preparation is required to get into a medical school, what medical school to go to and what happens when one gets there This little book, therefore, is a godsend not only to the prospective student who wishes to have his questions answered but also to the teacher of medicine who may be asked by a group of college undergraduates to tell the boys about medical education and why being a doctor is an absorbing occupation

The contents of the book are well arranged. Containing eleven chapters, the book begins with a description of today's process of medical education, continues with an account of medical school preparation (including what courses are to be taken and how students are selected) and ends with two chapters which hint as to what the future of medical practice is likely to be in the light of all the currents that nowadays are so clearly affecting its course.

The entire book is so simply written that any one can understand it. It deals with cold facts rather than with the romantic side of student life. It pretends to do no more than to offer to the young man who wishes to enter medicine a guide to the possibilities along the route that he must follow. It accomplishes this purpose with two of the essential virtues of persuasive writing, clarity and brevity.

Diagnosis and Management of Diseases of the Biliary Tract By R. Franklin Carter, M.D., F.A.C.S., Charles H. Greene, Ph.D., M.D., F.A.C.P., and John Russell Twiss, M.D., F.A.C.P. Price \$6.50. Pp. 432, with 90 illustrations. Philadelphia: Lea and Febiger, 1939.

The object of this book, as the authors state, is to set forth the principles of diagnosis and management of diseases of the biliary tract in as practical form as possible. To accomplish this end they have divided their subject matter into six parts: etiology, diagnosis, medical treatment, surgical treatment, results of surgical treatment and a final division of weight and dietary tables. Certain chapters were written by associates of the authors.

Great emphasis is placed on duodenal drainage. The authors clearly outline their technic and supplement their argument with photographs. The many illustrations add greatly to the value of this book. At the end of each chapter there is a more than adequate list of references.

In this manner the authors have succeeded in covering their field rather thoroughly.

Materia Medica, Drug Administration and Prescription Writing By Oscar W. Bethea. Fifth edition. Price, \$5. Pp. 577, with supplement 39 pp. Philadelphia: F. A. Davis, 1938.

The chapters on prescription writing are practical and take up all the points which the student must know. Part I, consisting of some 400 pages, considers alphabetically various therapeutic agents with reference to the properties, preparation, indications and dosage. There are many illustrative prescriptions. While much useful material is presented, undue space is given to semiobsolete preparations. Half a page, to mention one example, is given to juniper tar, regarding its uses the statement is made, "Has been used in the treatment of chronic nephritis, particularly when evidenced by edema." This sort of thing takes one back to nineteenth century medicine.

Ergebnisse der physikalisch-diatetischen Therapie Edited by H. Lampert, M.D., Director of the Institute of Physical Therapy at Frankfurt in association with W. Heupke, M.D., of Frankfurt, J. Kowarschuk, M.D., of Vienna, and J. Kuhnau, M.D., of Wiesbaden. Volume I. Pp. ix + 410, with 94 illustrations and many tables. Dresden and Leipzig: Verlag von Theodor Steinkopff, 1939.

For many years the Germans have, on the whole, been more seriously concerned with various forms of physical therapy than have physicians in the United States. The editors of this venture now sense the need of bringing together from time to time, in readable form, reports of the advancing knowledge in the contiguous fields of physical therapy, dietetic therapy and chemotherapy.

Volume I of the series starts off at a good pace. Exercise, heat, baths, climate, short wave therapy and diet each receive consideration. The editors have gathered together a group of articles, clearly presented by competent writers, on various uses of these methods in the treatment of different types of disease.

The section of the volume which deals with dietetic therapy is, to an American reader at least, somewhat commonplace. It is always stimulating, however, to interchange ideas with physicians from other parts of the world, thus, to read German ideas regarding diet in the therapy of cutaneous disease is informative, just as are German ideas in regard to such topics as diets for persons with diabetes and the peculiarities of protamine zinc insulin.

The articles which discuss diet in pregnancy and the treatment of hyperthyroidism are further off the beaten track. Dr. Gaetgens, of Leipzig, has produced some excellent graphs showing the tendencies toward various kinds of avitaminosis which pregnant women often display. Dr. May of Kreuth suggests the use of fluoride instead of iodide as a regulator of metabolic rate in hyperthyroidism—an interesting suggestion which might be studied further.

The entire volume is well indexed. Each chapter has an adequate bibliography. If future numbers keep up to the standard of the first volume, these *Ergebnisse* should have a successful future.

The Hospital Care of Neurosurgical Patients By Wallace B. Hamby, M.D.
Price \$2.00 Pp 118, with 24 illustrations Springfield, Ill., and Baltimore
Charles C. Thomas, 1939

Neurosurgeons are apt to have an almost ritualistic regard for detail in connection with the nursing of their patients. This is fitting, patients who have undergone neurosurgical operations are distinctly more ill than those in the general surgical service.

This monograph is designed to acquaint the nursing staff and the junior intern with the essentials of ward management of such patients. Preoperative and postoperative care, dressings, technics of the various diagnostic procedures and the objectives of the major surgical projects are dealt with. The author consistently keeps his audience in mind, and the studied simplicity of the presentation will be welcomed by those first approaching a field in which there still seems to be so much "black magic."

One difficulty is that although neurosurgeons feel very strongly about the various measures in management, there is little agreement among them. Any attempt at standardization seems a little ambitious. Hence we recommend that the house staff obey scrupulously every negative injunction the book imposes and as scrupulously refrain from initiating any measure it suggests without the specific consent of the surgeon.

Aparato circulatorio By Pedro Cossio. Second Edition. Pp 407, with 309 figures and 4 plates. Buenos Aires. Libreria y Editorial "El Ateneo," 1939.

This handsome book, finely printed and beautifully and profusely illustrated, may well invoke the praise of Dr. Cossio's North American colleagues. It is really an advanced treatise on physical diagnosis, after preliminary chapters on anatomy and physiology there are detailed discussions of physical examination, electrocardiography, roentgenologic diagnosis, measurement of venous pressure, circulation time and similar topics. Finally, there is an exhaustive section on the semiology of the arrhythmias. The material is well presented and, as mentioned above, the diagrams and the reproductions of roentgenograms, electrocardiograms and heart sound tracings are unsurpassed.

Die feinsten Blutgefasse des Menschen By Prof. Dr. Otfried Müller. Price, 60 marks. Pp 928, with 229 charts. Stuttgart. Ferdinand Enke, 1939.

This beautifully printed monograph of some nine hundred pages tells in minute detail about the state of the capillaries in all sorts of diseases. Many exquisite illustrations, for the most part in color, illustrate the text. This is indeed a monumental reference work even though the text makes heavy reading. The bibliography is poorly arranged.

EXPERIMENTS ON THE PROPERTIES OF THE EXTRINSIC FACTOR AND ON THE REACTION OF CASTLE

P FORMIJNE, M D
AMSTERDAM, NETHERLANDS

The effectiveness of an incubated mixture of meat and normal human gastric juice against anemia was first described by Castle¹ in 1929

In the original hypothesis it was assumed that a protein-like substance in the meat was split up by a proteolytic ferment of the normal gastric juice, either in vivo in the normal stomach or in vitro by incubation at 37 C, with formation of the effective antianemic substance. It was assumed by most authors that this newly formed substance was identical with the antianemic factor in liver, although this identity was not expressly stated by Castle.

The active factor in normal human gastric juice (called the intrinsic factor) was found to be thermolabile (it was destroyed by a temperature of 60 C in one-half hour). This intrinsic factor was not identical with either of the known ferments pepsin and rennin.

The active factor in the meat (called the extrinsic factor) was thermostable.

In 1933, Klein and Wilkinson² claimed to have proved the formation of the antianemic factor in liver by incubation of meat and hog gastric mucosa in vitro. This claim was based on two types of experiments. In the first type the incubated mixture of meat and hog mucosa (containing the intrinsic factor) was heated to 60 or 65 C for one-half hour without loss of activity.

These experiments have been criticized by Castle. He showed that heating of the incubated mixture at 80 C for one-half hour invariably destroyed the activity. This temperature would not affect the antianemic liver factor if it had been formed in the incubated mixture.

From the Department of Internal Medicine, the University of Amsterdam,
Prof Dr I Snapper, Director

1 Castle, W B. *Am J M Sc* **178** 748, 1939

2 Klein, L, and Wilkinson, J F. *Biochem J* **28** 1684, 1934

Castle, Heath, Strauss and Heinle³ attributed the positive results obtained by Klein and Wilkinson² to the too low degree of heating and to a possible slight protective activity of the proteins of the meat on the intrinsic factor

In the second experiment of Klein and Wilkinson an attempt was made to isolate the newly formed antianemic liver factor from the incubated mixture, they added 70 per cent alcohol, filtered the mixture and concentrated the filtrate in vacuo. Finally, the concentrated filtrate was precipitated with 96 per cent alcohol. The precipitate was dissolved in water and injected into a patient with pernicious anemia, with a subsequent increase of reticulocytes, hemoglobin and erythrocytes. This result cannot be accepted as proof of the effectiveness of their product, because the reticulocytic peak occurred only on the nineteenth day of treatment, much too late to indicate a real effectiveness of the preparation injected.

In a recent article, Wilkinson, Klein and Ashford⁴ described an experiment of the same type. Meat was incubated with human stomach tissue, and a product isolated in the manner described was given orally to a patient with pernicious anemia. A reticulocytic crisis on the eighth day and a rather slow increase of hemoglobin and erythrocytes resulted. Although this experiment has much more value than those previously described, it was not controlled by ingestion of the same amount of normal human stomach tissue without incubation with meat.

In 1936, Greenspon⁵ criticized Castle's findings. He claimed that the antianemic principle is secreted by the stomach but that it is destroyed by peptic digestion and is protected against this destruction by addition of the proteins of the meat. This criticism has been refuted by Castle and others. It was shown that neutralized gastric juice alone is inactive if certain precautions are taken.

During these controversies some new interesting facts have been described, mainly by Castle, Heath, Strauss and Heinle³

1 The mixture of meat and gastric juice was effective without incubation

2 The mixture of meat and gastric juice was effective at a neutral reaction, whereas it was not effective if the reaction was strongly acid (p_H 1.8 to 2.5)³

3 When meat and gastric juice were given separately with an interval of no more than six hours a positive therapeutic effect was observed

³ Castle, W. B., Heath, C. W., Strauss, M. B., and Heinle, R. W. *Am J M Sc* **194** 618, 1937

⁴ Wilkinson, J. F., Klein, L., and Ashford, C. A. *Quart J Med* **7** 555, 1938

⁵ Greenspon, E. A. Nature of Antipernicious Anemia Principle in Stomach Method to Improve Stomach Preparations, *J A M A* **106** 266 (Jan 25) 1936

As a result of these findings, the original hypothesis of Castle had to be reconsidered. Castle stated recently that the site and mode of interaction between the extrinsic factor and the intrinsic factor are not yet known, although the site is probably in the gastrointestinal tract. Taylor, Castle, Heinle and Adams⁶ demonstrated a close chemical resemblance between the intrinsic factor and a proteolytic ferment of the gastric juice acting at neutral reaction. Obviously the identity of the intrinsic factor with this proteolytic ferment is considered in this article, although it is not expressly stated. Acceptance of this identity would imply the formation of a new intermediary substance, which finally would be transformed into the antianemic liver factor.

PLAN OF INVESTIGATION

The experiments reported in this paper were started in 1936. They were based on the theory, prevailing at that time, of an *in vitro* formation of the antianemic liver factor in the gastric juice-meat mixture. It was thought probable that the chemical behavior of the extrinsic factor would be changed by transformation into the antianemic liver factor. A comparative study of the chemical properties of the extrinsic factor and the liver factor was planned.

Isolation and study of the liver factor have been advanced by many investigators, but a systematic investigation of the extrinsic factor has not been published. Castle demonstrated the solubility of the extrinsic factor from marmite (an autolyzed yeast extract) in 80 per cent alcohol. In the present observations this principle was applied to the extrinsic factor of meat. It was found possible to obtain extracts which were active after addition of normal gastric juice in the following manner:

Two hundred and fifty grams of beef was minced and mixed with a small quantity of water. To the resulting meat pulp concentrated alcohol was added until a concentration of 70 per cent was reached. The mixture was kept overnight and filtered next morning. The filtrate was distilled *in vacuo*. In the following observations, the resulting white turbid fluid will be called 70 per cent alcoholic extract of meat.

Normal human gastric juice which had been carefully neutralized immediately after removal from the stomach and had been kept in an ice box if necessary (for a maximum of three or four days) was used in all experiments.

Incubation for four hours was applied in experiments 1 and 2. In the subsequent experiments of the first series the incubation, which appeared to be unnecessary, was omitted.

In the first series of experiments the properties of the extrinsic factor in meat were studied. In the second series the nature of the reaction between the extrinsic factor and the intrinsic factor was investigated.

In all experiments which will be reported as test cases the patients had typical pernicious anemia in relapse, associated with achylia gastrica which was refractory to histamine (except the patient in experiment 3). A survey of the cases of these patients is given in table 1. Further clinical details will not be reported, as a typical response to therapy was obtained in all cases, either by administration of mixtures of the extrinsic and the intrinsic factor or by injection of liver preparations. In order to exclude ingestion of large amounts of the extrinsic factor, during the

⁶ Taylor, F. H. L., Castle, W. B., Heinle, R. W., and Adams, M. A. *J. Clin. Investigation* **17** 335, 1938.

test periods no meat was included in the diet of the patients. All preparations were given in the morning to the fasting subject, and a light breakfast without tea was allowed one and one-half hours after the ingestion.

PROPERTIES OF EXTRINSIC FACTOR

EXPERIMENT 1 (patient P. G.) —In the first period, a mixture of washed human erythrocytes (30 cc) with 150 cc of gastric juice was administered daily for nineteen days by stomach tube, without therapeutic effect. The meaning of this negative result will be discussed in a forthcoming article. The therapeutic inactivity of gastric juice, alone or mixed with inactive proteins, is shown by this first period.

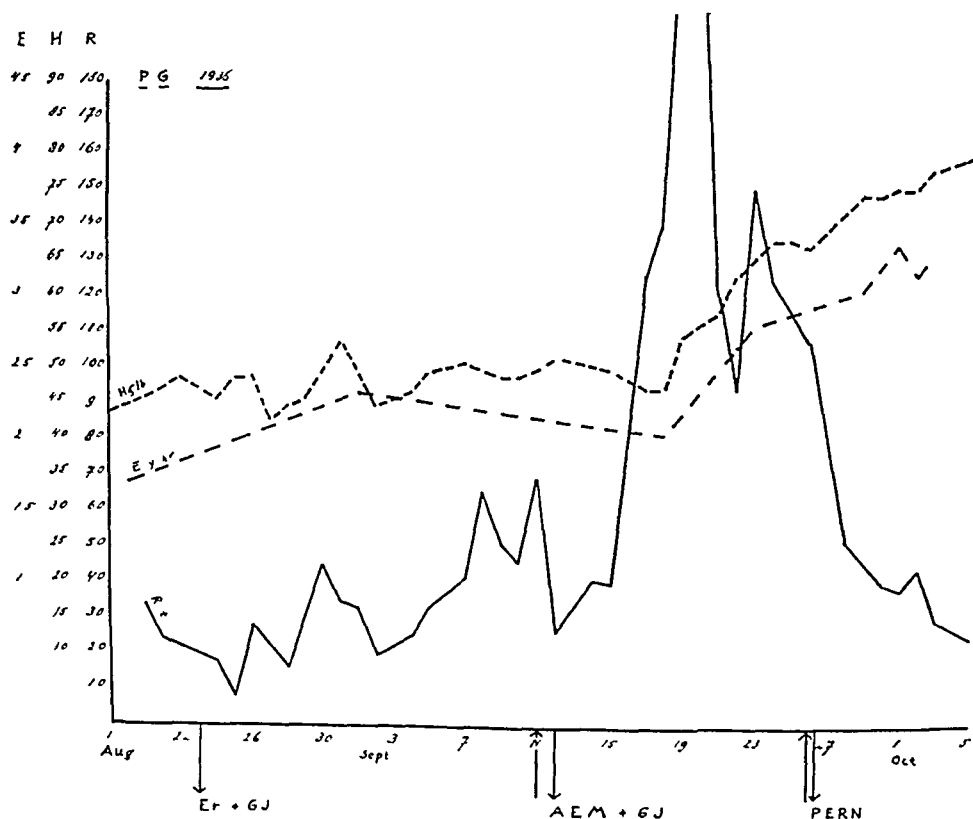


Chart 1 (experiment 1) —In the first period, 30 cc of washed centrifuged human erythrocytes (Er) and 130 cc of gastric juice (GJ) was given daily from Aug 23 to Sept 11, 1936. In the second period, 70 per cent alcoholic extract of meat (AEM) and 150 cc of gastric juice was given daily from September 12 to 26. Pernaemon was injected daily from September 26. (In this and in the following charts, gastric juice is indicated by the letters GJ, alcoholic extract of meat by the letters AEM, and injection of the liver preparation pernaemon by the letters PERN.)

In the second period, a mixture of 70 per cent alcoholic extract of meat (250 Gm) and 150 cc of gastric juice, incubated for four hours at 37 C, was administered daily to the fasting subject. A typical reticulocyte crisis with an increase of hemoglobin and erythrocytes followed (chart 1). When the reticulocyte crisis had disappeared, injections of a liver concentrate (pernaemon) were given daily, without further effect on the reticulocytes. A maximum therapeutic response was obtained in this manner.

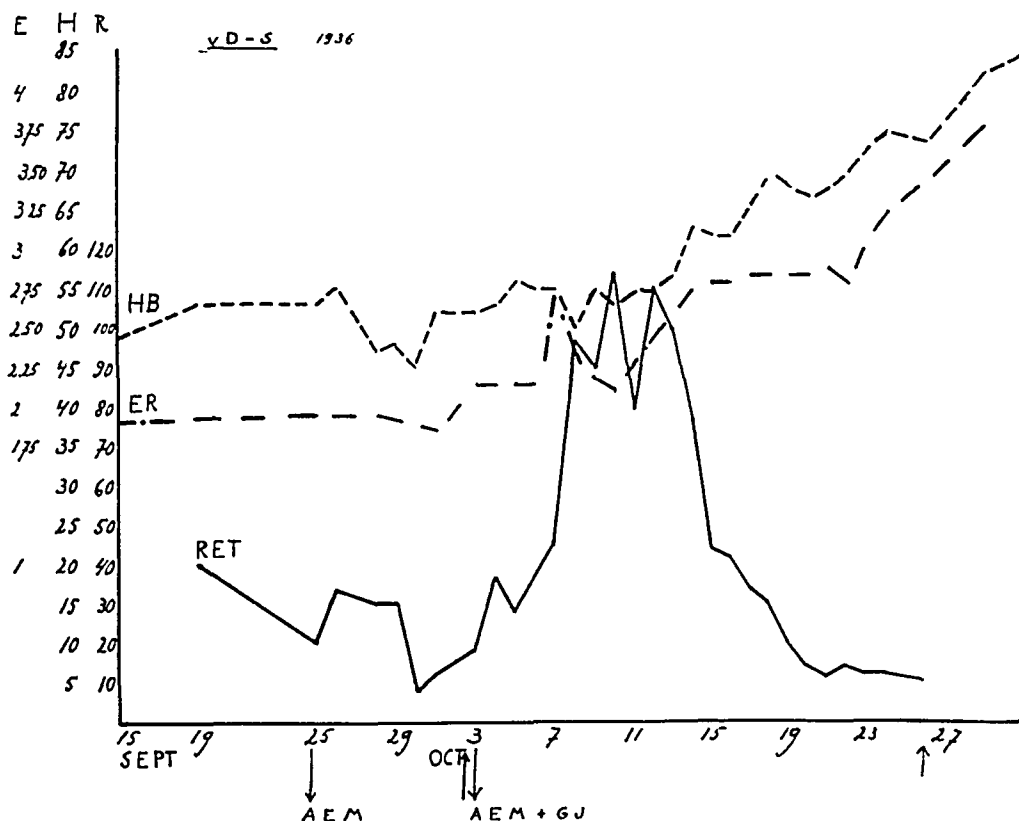


Chart 2 (experiment 2) —In the first period, 70 per cent alcoholic extract of meat (250 Gm) was given daily from Sept 24 to Oct 2, 1936. In the second period, 70 per cent alcoholic extract of meat (250 Gm) and 50 cc of gastric juice was given daily from October 3 to 26.

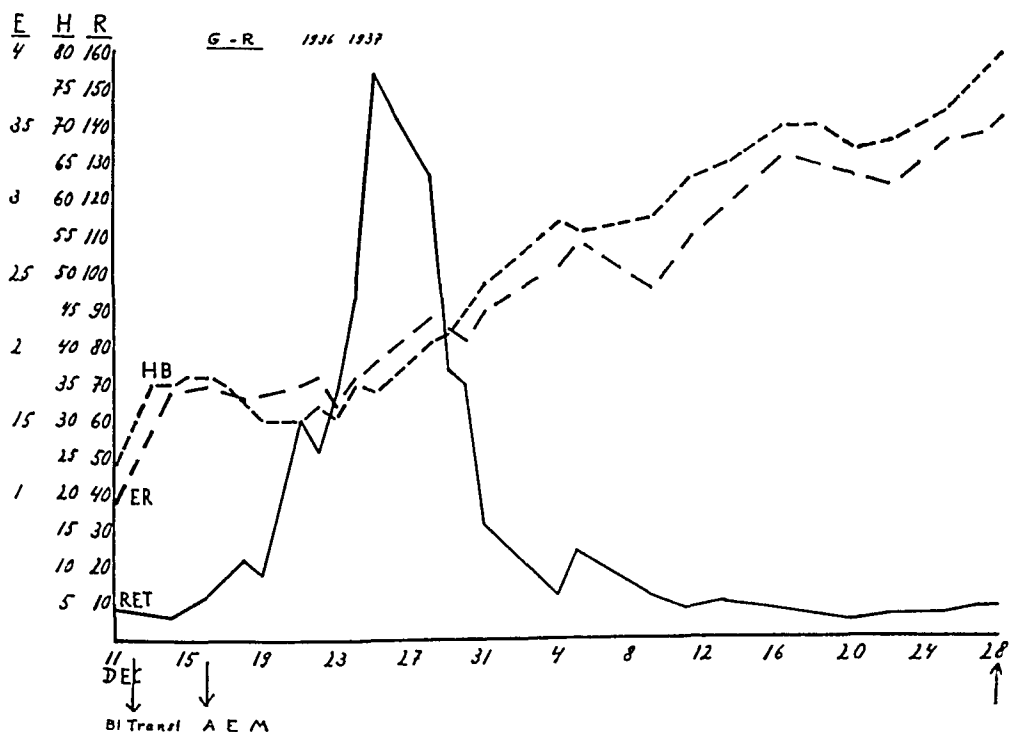


Chart 3 (experiment 3) —A blood transfusion was given on Dec 12, 1936. Seventy per cent alcoholic extract of meat (250 Gm) was given daily from Dec 16 to Jan 28, 1937.

EXPERIMENT 2 (patient v D S) —In the first period, 70 per cent alcoholic extract of meat (250 Gm), without gastric juice, was given. There was no therapeutic effect. In the second period, 70 per cent alcoholic extract of meat (250 Gm) mixed with 50 cc of gastric juice incubated for four hours at 37 C was administered daily. Again a marked therapeutic result was seen, the typical reticulocyte crisis was followed by a marked increase of hemoglobin and erythrocytes (chart 2).

EXPERIMENT 3 (patient G R) —In this patient severe anemia developed during pregnancy. She came into the ward in a severely anemic condition immediately after delivery. The blood picture was typical of pernicious anemia. Megaloblasts were present. The color index was elevated. However, free hydrochloric acid was found in the stomach. The diet had been insufficient during pregnancy, the patient had eaten scarcely any meat. The condition was considered to be a typical pernicious anemia of pregnancy, caused by relatively insufficient ingestion of the extrinsic factor. A blood transfusion was given, followed by administration of a mixture of alcoholic extract of meat (250 Gm) without gastric juice. In contrast with the results in experiment 2, a typical therapeutic response was seen, which was attributed to ingestion of the extrinsic factor alone by this patient with normal gastric juice. It was considered improbable that this response had anything to do with the preceding blood transfusion (chart 3).

Comment on Experiments 1, 2 and 3 —The presence of the extrinsic factor in the 70 per cent alcoholic extract of meat is proved by these experiments. The therapeutic response of the mixture with only 50 cc of gastric juice in experiment 2 facilitated the subsequent experiments. In most cases 75 cc of gastric juice was used.

In the following experiments an attempt was made to precipitate the extrinsic factor with 96 per cent alcohol, without success. Not all experiments with negative results are reported. The only questionable response was observed in the following experiment.

EXPERIMENT 4 (patient P F) —Seventy per cent alcoholic extract of meat (500 Gm) was treated with absolute alcohol until a concentration of 96 per cent was reached and then was filtered. The precipitate (*a*) was dissolved in water, the filtrate (*b*) was distilled in vacuo. In the first period, the precipitate, *a* (of 500 Gm of meat), was mixed with 100 cc of gastric juice and administered daily to the patient for ten days. On the eleventh day a moderate reticulocyte response, without increase of hemoglobin or erythrocytes, followed. It is uncertain whether this late reticulocyte crisis was caused by the presence of a small amount of extrinsic factor in the precipitate.

In the second period, from the eleventh to the twentieth day, the filtrate, *b* (of 500 Gm of meat), mixed with 100 cc of gastric juice, was administered daily without any further effect.

In the third period, the 70 per cent alcoholic extract of meat (250 Gm) with 75 cc of gastric juice was administered daily for four days. The condition of the patient did not allow continuation of the experiment.

On injection of a liver concentrate a typical therapeutic response was obtained.

EXPERIMENT 5 (patient R V) —The 70 per cent alcoholic extract of meat (250 Gm) was treated with 96 per cent alcohol as described for experiment 4. The precipitate (a) and the filtrate (b) were reunited and mixed with 75 cc of gastric juice. This mixture was administered daily to the patient, without any result. On injection of pernaemon a typical therapeutic response was seen (chart 5).

Comment on Experiments 4 and 5—Destruction of the extrinsic factor by 96 per cent alcohol is clearly shown by experiment 5. The possibility that this destruction is not complete must be accepted on the

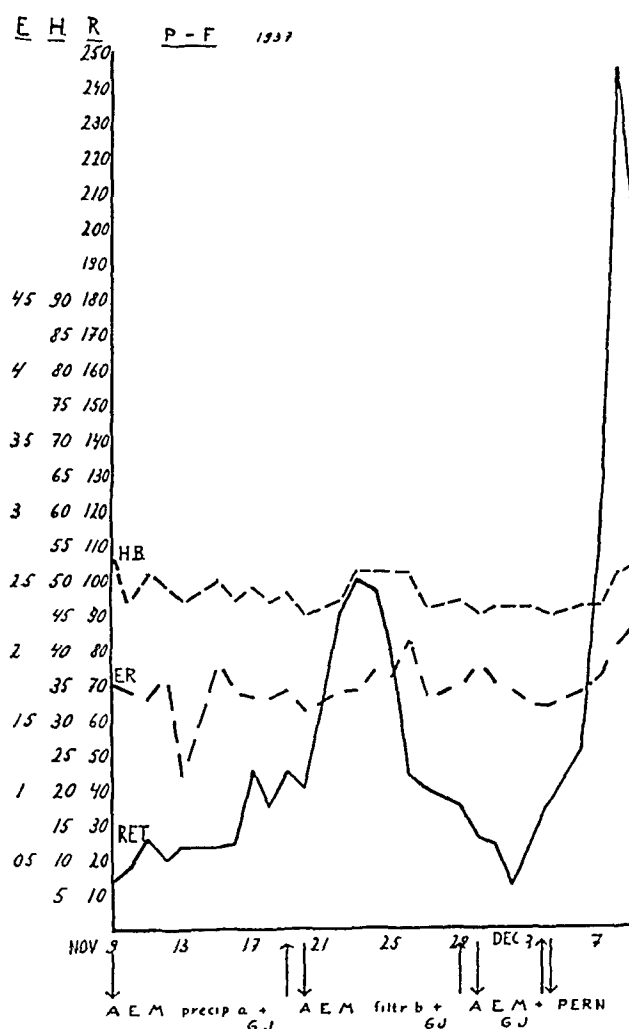


Chart 4 (experiment 4) —Seventy per cent alcoholic extract of meat (500 Gm) was treated with 96 per cent alcohol (precipitate a and filtrate b). In the first period, precipitate (a) and 100 cc of gastric juice was given daily from Nov 9 to 19, 1937. In the second period, filtrate (b) and 100 cc of gastric juice was given daily from November 20 to 29. In the third period, 70 per cent alcoholic extract of meat (250 Gm) and 75 cc of gastric juice was given daily from November 30 to December 4. Pernaemon was injected daily from December 4.

dubious evidence of experiment 4, with doubled quantities of the precipitate. For the study and isolation of the extrinsic factor this precipitation was deemed to be unfruitful. The sensitivity of the extrinsic factor to 96 per cent alcohol was quite unexpected.

The white turbidity of the alcoholic extract (after distillation in vacuo) suggested the presence of fats and lipoids, which inhibited to a certain extent the study of the extract. In the next experiment an attempt was made to remove the fats by ether extraction. In the same experiment the concentration of alcohol used in the first extraction was raised to 80 per cent.

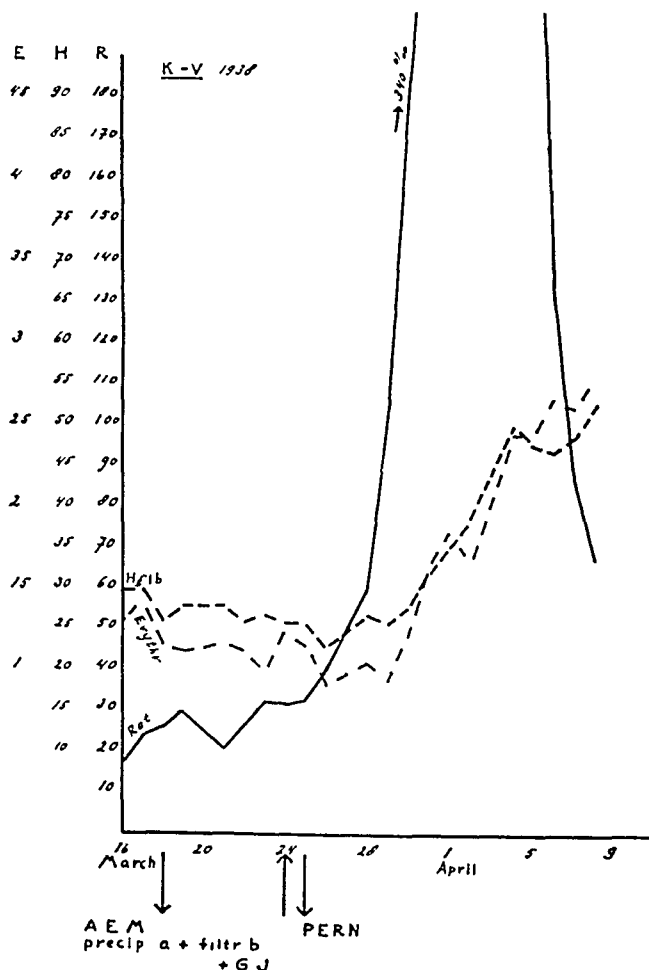


Chart 5 (experiment 5) —Seventy per cent alcoholic extract of meat (250 Gm) was treated with alcohol, 96 per cent the precipitate (a) and the filtrate (b) were reunited (see text), $a + b$ and 75 cc of gastric juice was given daily from March 18 to 24, 1938. Pernaemon was injected daily from March 25.

EXPERIMENT 6 (patient L. P.) —The 80 per cent alcoholic extract of meat (250 Gm) was extracted with ether. The ether was separated from the fluid. The remaining fluid was centrifuged to remove a white precipitate at the bottom. The resulting slightly turbid fluid was mixed with 75 cc of gastric juice and administered daily to the patient. An intense reticulocyte crisis (maximum, 28 per cent) and a fast rise in the concentration of hemoglobin and erythrocytes indicated a maximal response.

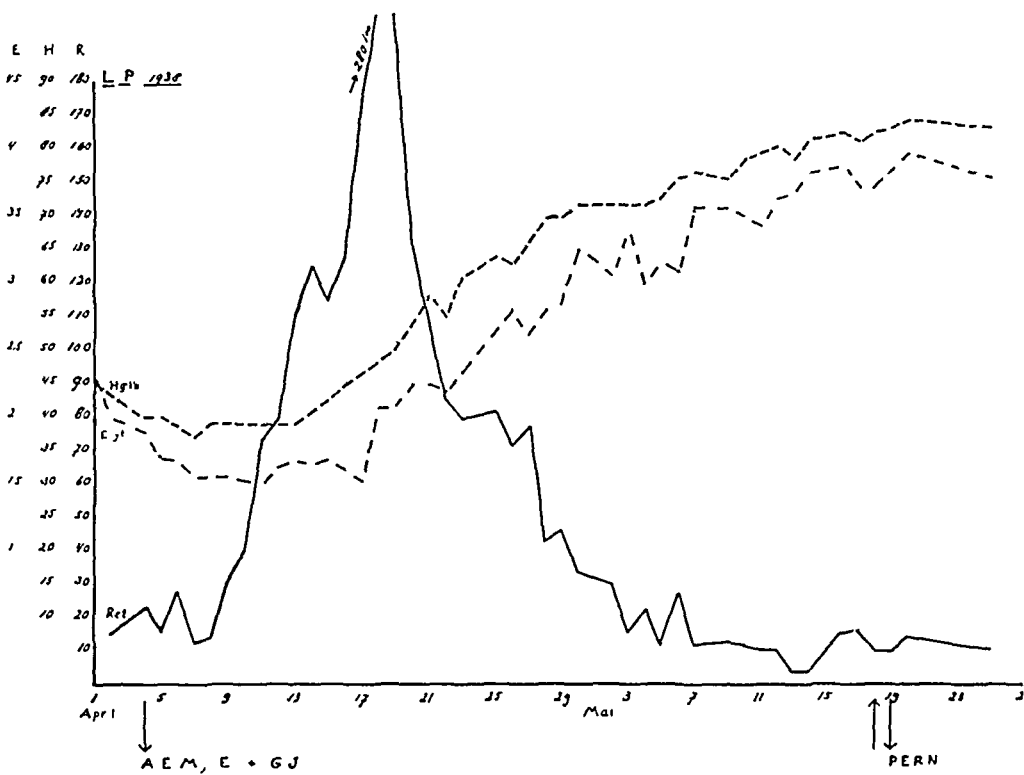


Chart 6 (experiment 6)—Eighty per cent alcoholic extract of meat (250 Gm) extracted with ether (indicated by the letters A E M, E) and 75 cc of gastric juice was given daily from April 4 to May 18, 1938 Pernaemon was injected daily from May 19

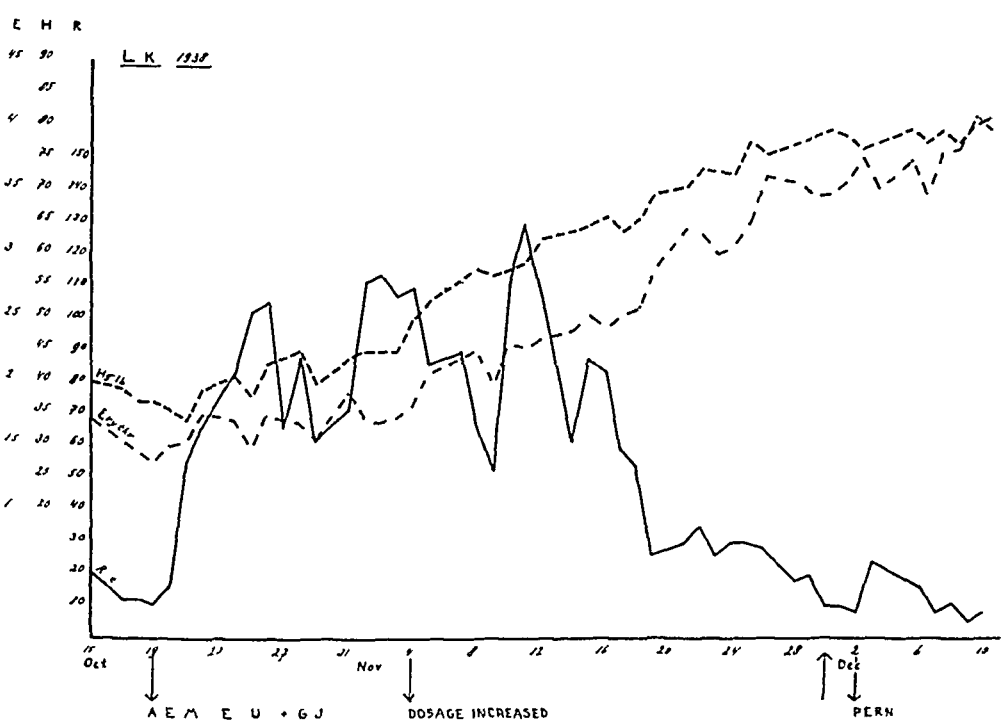


Chart 7 (experiment 7)—Eighty per cent alcoholic extract of meat (330 Gm) extracted with ether and ultrafiltered (indicated by the letters A E M, E, U) and 75 cc of gastric juice was given daily from Oct 19 to Nov 4, 1938 The same preparation, originating from 500 Gm of meat and 75 cc of gastric juice was given daily from November 4 to 30 Pernaemon was injected daily from December 2

Comment—The ether-soluble substances can be removed from the alcoholic extract without loss of activity. The activity of an 80 per cent alcoholic extract of meat was proved in the same experiment.

The results of ultrafiltration on extracts containing the extrinsic factor have not been reported in the literature. The following experiment is of importance in deciding finally whether the extrinsic factor may be a protein-like substance, as was originally assumed by Castle. This experiment was made possible by the preceding ether extraction.

EXPERIMENT 7 (patient L. K.)—The 80 per cent alcoholic extract of meat (330 Gm.) was extracted with ether. The remaining watery fluid was ultrafiltered in collodion sacs. The ultrafiltrate was mixed with 75 cc. of gastric juice and administered to the patient daily. A clearcut but irregular reticulocyte crisis followed, but there was only a slow rise of the concentration of hemoglobin and erythrocytes. Consequently, on the twentieth day the daily dose of ultrafiltrate was raised to a dose obtained from 500 Gm. of meat mixed with the same amount (75 cc.) of gastric juice. A new reticulocyte crisis followed, together with a fast increase of hemoglobin and erythrocytes.

Comment—The experiment clearly shows that the extrinsic factor passes through an ultrafilter. During this procedure a loss of activity is apparent. In a second experiment, not reported in detail, exactly the same results were obtained—a positive effect of the ultrafiltrate, but only in a higher dose than that of the original extract.

The cause of this loss of activity during ultrafiltration was not clear at first. The majority of the substances present in the original alcoholic extract passed through the ultrafilter, as will be seen from table 1. Only a small fraction of the fluid remained in the filter. The possibility of partial absorption of the extrinsic factor by the collodion sac was considered. In another experiment, which will be reported later (experiment 15, third period), physiologic solution of sodium chloride was added to the remainder of the fluid in the collodion sacs, and the ultrafiltration was then continued. The ultrafiltrate obtained was mixed with the first ultrafiltrate and with 75 cc. of gastric juice and administered to the patient. The combined ultrafiltrates of 330 Gm. of meat were given in this manner. A marked therapeutic response was seen. This experiment suggests the possibility that the amount of the effective substance present in the ultrafiltrate is increased by washing.

The next step in analysis of the extrinsic factor was precipitation of the alcoholic meat extract with saturated ammonium sulfate. Less than one tenth of the substance originally present in the extract was precipitated in this manner.

TABLE 1—Data on Patients with Pernicious Anemia Used as Test Subjects

Experi- ment No	Initials of Patient	Sex	Age	Free HCl in Stomach (with His- tamine Injection)	Initial Blood Picture							Complications
					Hemo- globin, %	Red Blood Cells, Millions per Cu Mm	Reticu- locytes, %	Aniso- cytosis	Poikilo- cytosis	Normo blasts	Megalo blasts	
1	P G	M	43	—	44	1 70	3 4	++	++	—	—	
2	V D S	F	54	—	19	1 92	4 0	++	++	—	1	
3	G R	F	28	+	24	0 96	0 8	+++	+++	4	3	
4	P S	F	57	—	55	1 94	0 4	+	+	1	—	
5	K V	F	55	—	33	1 32	1 8	++	++	2	1	Pernicious anemia of pregnancy
6	L P	M	55	—	33	1 33	2 0	+	+	5	3	
7	L K	M	58	—	43	1 56	2 0	+	+	1	—	Tropical sprue
8	S M	M	57	—	50	1 79	0 4	+++	+	—	—	Auricular fibrillation
9	J P	M	60	—	68	2 92	0 8	+	+	1	—	
10	J S	M	61	—	67	1 72	3 8	+	+	1	—	
11	B K	F	62	*	34	1 71	0 6	++	++	—	1	
12	K S	F	60	—	26	1 30	1 2	++	++	4	3	Polyneuritis
13	J B	M	81	—	44	1 44	0 6	+	+	—	—	
14	V B M	F	37	—	31	1 23	1 6	+++	+++	4	8	
15	J R	M	46	—	44	1 17	5 0	+	+	9	—	

* Investigation of the stomach was refused by the patient. In 1933 there was no free hydrochloric acid, no histamine was given

EXPERIMENT 8 (patient S M) —The 80 per cent alcoholic extract of meat (330 Gm) was extracted with ether and afterward saturated with ammonium sulfate. The precipitate was separated by decantation and centrifugation and finally dissolved in water. This solution was mixed with 75 cc of gastric juice and administered daily to the patient.

A moderate reticulocytic rise was observed, with a maximum on the tenth day, but only a slight increase of the hemoglobin values occurred, without any change in the number of erythrocytes. On the fifteenth day the amount of precipitate was increased one and one-half times (e g, the precipitate originating from 500 Gm of meat was given daily). A second reticulocyte crisis was seen, together with a steady increase of hemoglobin and erythrocytes. About one month afterward an injection of pernaemon was given, without any effect on the reticulocytes.

EXPERIMENT 9 (patient L P) —In this experiment a high initial value for hemoglobin was present, therefore, marked results could not be expected.

In the first period, gastric juice was treated with 70 per cent alcohol, and the resulting fractions were reunited, 80 per cent alcoholic extract of meat (250 Gm) was added. The mixture was administered to the patient. The reader is referred to experiment 15 (first period) for a more detailed description and for a discussion of its meaning. The result was considered to be negative. The slight increase in number of reticulocytes, which was almost maximal on the fourth day, could not be attributed to this preparation, for it was too early. At the same time a fall in the number of erythrocytes occurred.

In the second period, beginning on the eleventh day, the ammonium sulfate precipitate from the 80 per cent alcoholic extract of meat (500 Gm), as described for experiment 8, was mixed with 75 cc of gastric juice and administered daily to the patient. A moderate reticulocyte crisis with a marked increase of hemoglobin and erythrocytes followed.

EXPERIMENT 10 (patient J S) —In the first period, a fraction of the ammonium sulfate precipitate (the nonultrafiltrable rest) was given, together with 75 cc of gastric juice. This fraction seemed to be inactive, although a slight increase of reticulocytes was present on the eighth day, a slight but steady decrease of hemoglobin and erythrocytes occurred.

In the second period, beginning on the fourteenth day, the ammonium sulfate precipitate from the 80 per cent alcoholic extract of meat (500 Gm), as described for experiment 8, was mixed with 75 cc of gastric juice and administered daily to the patient. A marked reticulocyte crisis with a maximum on the eleventh day followed, but there was no corresponding increase of hemoglobin and erythrocytes. On the thirty-fourth day an injection of the liver extract pernaemon was given, a second sharp reticulocyte crisis with increase of erythrocytes and hemoglobin followed.

Comment on Experiments 8, 9 and 10 —In these experiments the result of the ammonium sulfate precipitate of the 80 per cent alcoholic meat extract was studied. In experiment 8 it was found that the precipitate from 330 Gm of meat daily was insufficient for a good therapeutic result. The precipitate from 500 Gm of meat daily gave a good result in this patient.

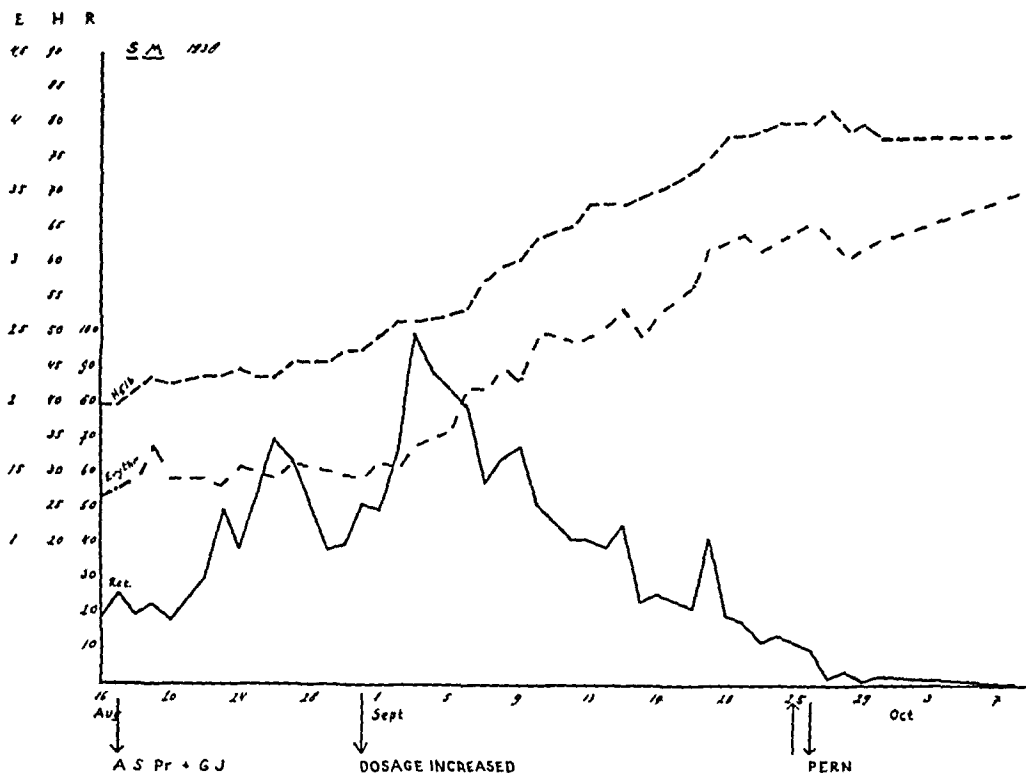


Chart 8 (experiment 8) —Eighty per cent alcoholic extract of meat (330 Gm) extracted with ether, precipitated by saturation with ammonium sulfate (indicated by the letters A S Pr) and 75 cc of gastric juice was given daily from Aug 17 to 31, 1938 The same preparation, originating from 500 Gm of meat and 75 cc of gastric juice, was given daily from August 31 to September 25 Pernaemon was injected daily from September 26

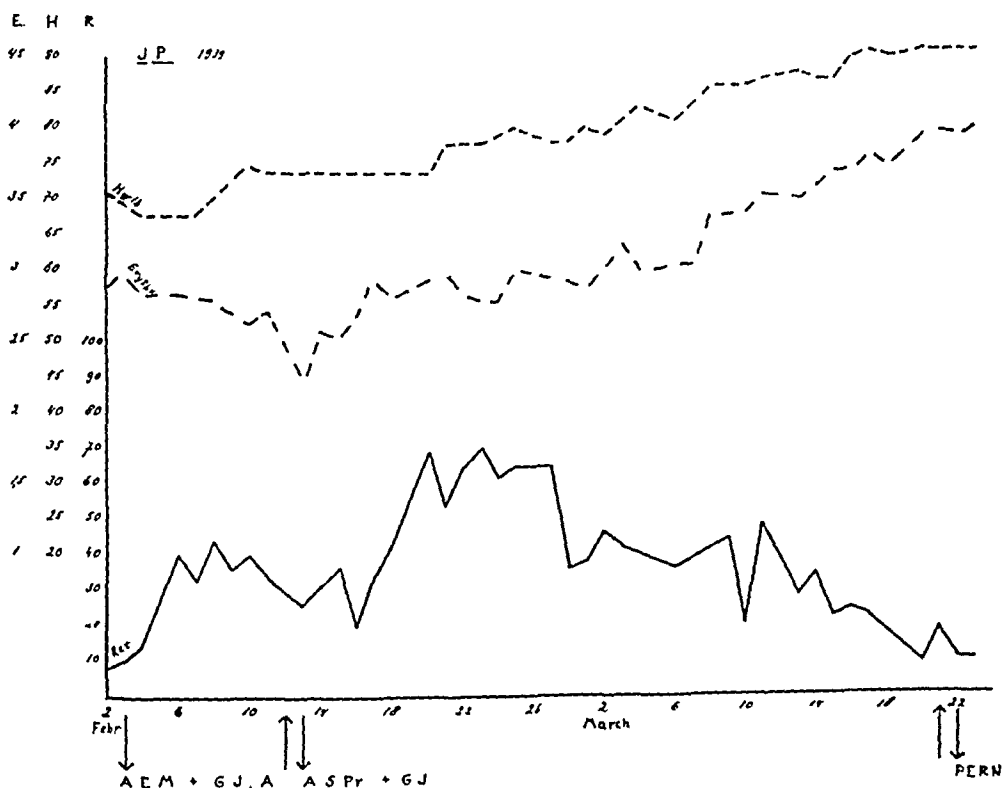


Chart 9 (experiment 9) —In the first period, 80 per cent alcoholic extract of meat (250 Gm) and 75 cc of gastric juice (treated with 70 per cent alcohol, indicated by the letters G J, A) was given daily from Feb 3 to 12, 1939 In the second period, ammonium sulfate precipitate (A S Pr) from 500 Gm of meat (same preparation as in experiment 8) and 75 cc of gastric juice was given daily from February 13 to March 21 Pernaemon was injected daily from March 22

In experiment 9 the ammonium sulfate precipitate from 500 Gm of meat was administered daily, with a satisfactory therapeutic result

In experiment 10 the same amount of ammonium sulfate precipitate gave a marked reticulocytic crisis, but without a rise in concentration of hemoglobin and erythrocytes

These experiments show that the extrinsic factor is present in the ammonium sulfate precipitate but that loss of more than 50 per cent of the active substance occurs. It was considered probable that in experiment 10 a further increase in the amount of precipitate daily

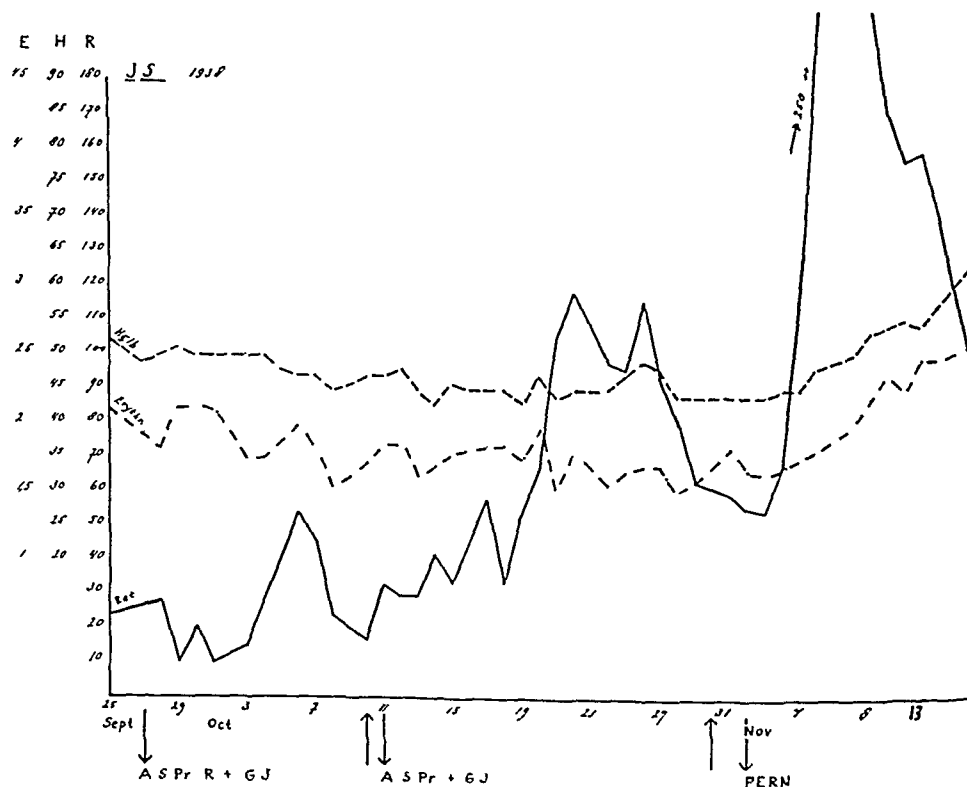


Chart 10 (experiment 10) —The ammonium sulfate precipitate originating from 500 Gm of meat (same preparation as in experiment 8) was ultrafiltered and separated into an ultrafiltrate and a nonultrafiltrable rest (A S Pr, R). In the first period, the latter preparation (A S Pr, R) and 75 cc of gastric juice was given daily from Sept 27 to Oct 10, 1938. In the second period, the ammonium sulfate precipitate originating from 500 Gm of meat (A S Pr) and 75 cc of gastric juice was given daily from October 10 to 30. Pernaemon was injected daily from November 1.

administered would have given a good therapeutic effect, but this experiment could not be extended any longer.

An investigation of the fractions obtained by ultrafiltration and by precipitation with ammonium sulfate showed that the nonultrafiltrable rest contained the major part of the substances which were precipitated

by ammonium sulfate. This fact is demonstrated in table 2. In this table the amount of substance present in the various fractions of a single extract is shown as an example.

Similar values were obtained with other extracts. The figures in table 2 show that 80 per cent of the small precipitate obtained with ammonium sulfate did not pass an ultrafilter, the extrinsic factor should be present in the very small fraction of the precipitate which passed the ultrafilter. Daily administration of this fraction (e. g., the ultrafiltrate of the ammonium sulfate precipitate obtained from 500 Gm. of meat) mixed with 75 cc. of gastric juice to a patient with pernicious anemia did not have any effect (experiment not reported in detail). The nonultrafiltrable rest of the ammonium sulfate precipitate was mixed

TABLE 2—*Weight of Fractions Obtained in the Foregoing Experiments*

1 Kg. of Meat	Dry Substance, Gm./Kg.	Therapeutic Response
80% alcoholic extract	26.34	+
80% alcoholic extract after extraction with ether	19.44	+
Ether soluble substances	7.00	
80% alcoholic extract extracted with ether and ultrafiltered, ultrafiltrate	17.04	+
80% alcoholic extract extracted with ether and ultrafiltered, non-ultrafiltrable rest	1.70	
80% alcoholic extract extracted with ether and ultrafiltered, non-ultrafiltrable rest saturated with ammonium sulfate, precipitate	0.72	
80% alcoholic extract extracted with ether and saturated with ammonium sulfate, precipitate	1.09	+
Ammonium sulfate precipitate of 80% alcoholic extract extracted with ether and ultrafiltered, ultrafiltrate	0.13	—
Ammonium sulfate precipitate of 80% alcoholic extract extracted with ether and ultrafiltered, nonultrafiltrable rest	0.91	—

with 75 cc. of gastric juice and administered during the first period of experiment 10, without clearcut effect. The lack of activity of these fractions is probably caused by the progressive loss of active substance in each fractionation, especially in the precipitation with ammonium sulfate. It is possible that the active substance is not truly precipitated by ammonium sulfate but is only partially absorbed by the other precipitated substances.

In the foregoing experiments an analysis of the extrinsic factor was attempted. In the following series of experiments Castle's reaction was analyzed.

ANALYSIS OF CASTLE'S REACTION

An attempt was made to isolate the antianemic substance from the incubated mixture of meat and gastric juice, as has been done by Wilkinson and Klein.

EXPERIMENT 11 (patient B. K.)—To the incubated mixture of alcoholic extract of meat (1 Kg.) and 400 cc. of gastric juice, concentrated alcohol was added until a con-

centration of 70 per cent was reached. The fluid was filtered and the filtrate concentrated in vacuo to a small volume. To the concentrate absolute alcohol was added until a concentration of 96 per cent was reached. The precipitate was collected, was dissolved in isotonic salt solution and, after careful sterilization by pasteurization at 70 C, was administered to the patient by intramuscular injection. The whole amount was given in four days. The result was wholly negative. There was no response of reticulocytes, hemoglobin or erythrocytes.

Comment—The antianemic liver factor is soluble in 70 per cent alcohol and is precipitated by 96 per cent alcohol. These properties

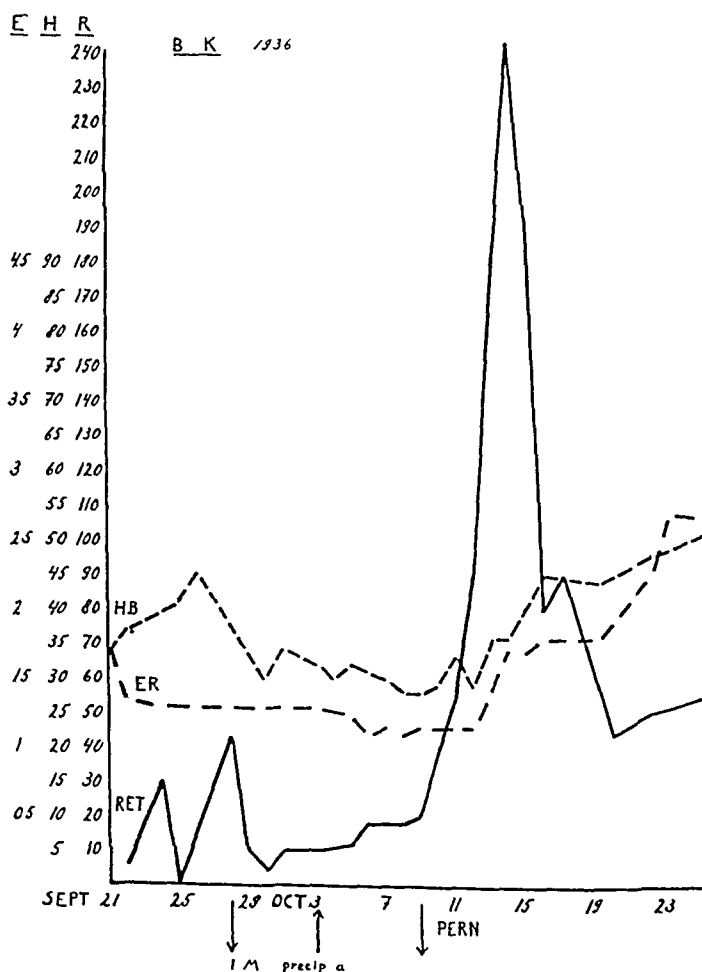


Chart 11 (experiment 11)—Precipitation of the incubated mixture of alcoholic extract of meat (1 Kg) and gastric juice (400 cc) with concentrated alcohol. The preparation, indicated by the letters I M, precip a, was given divided in several doses by intramuscular injection from Oct 28 to Nov 3, 1936. Pernaemon was injected daily from November 9.

were used to analyze the incubated mixture of meat and gastric juice for newly formed antianemic liver factor. The injection of the fraction thus isolated gave negative results, contrasting with the positive results obtained with a similar product by Wilkinson and Klein. The

possibility of loss of activity of the product during preparation for injection was considered

EXPERIMENT 12 (patient K S) —The incubated mixture of meat (250 Gm) and gastric juice was treated with 70 per cent alcohol and afterward with 96 per cent alcohol as described for experiment 11 The resulting precipitate was dissolved in isotonic salt solution and administered daily to the patient by mouth Again the effect was absolutely negative

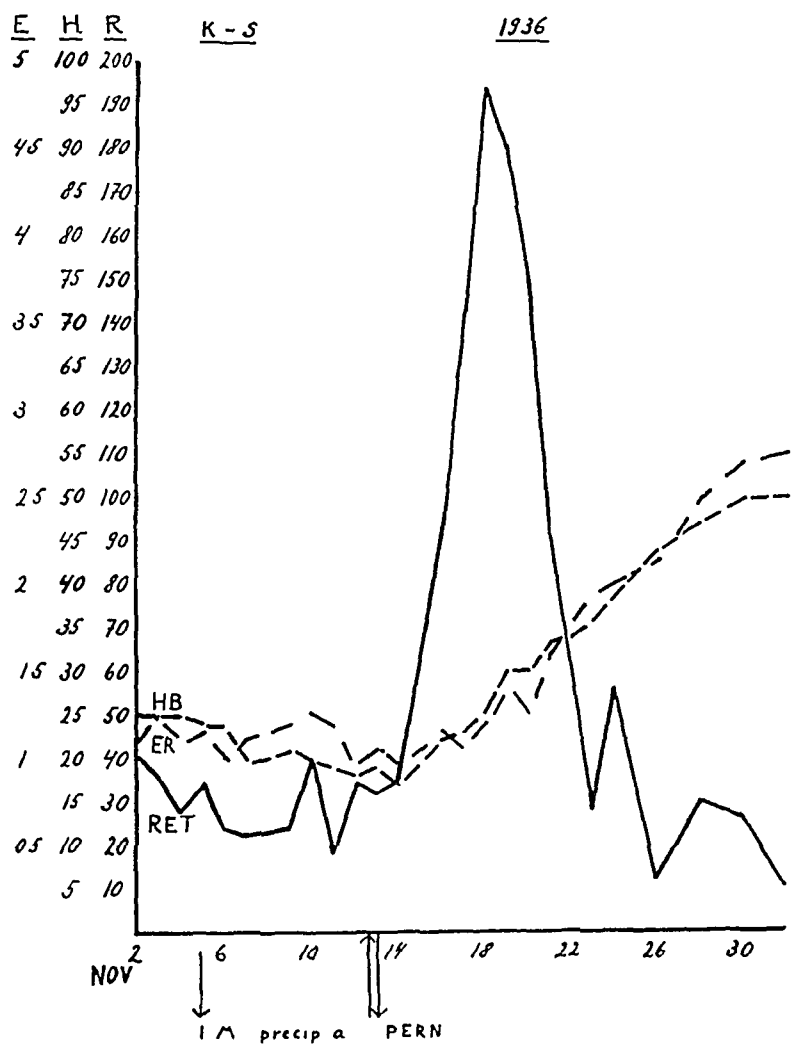


Chart 12 (experiment 12) —The same preparation as in experiment 11 (from 250 Gm of meat), indicated by the letters IM, precip a, was given daily by mouth from Nov 5 to 13, 1936 Pernaemon was injected daily from November 13

Comment —This experiment, together with experiment 11, demonstrates that in the 96 per cent alcoholic precipitate obtained from the incubated mixture no therapeutically active amount of liver factor is present

In the next experiment the number of manipulations was still more restricted by omission of precipitation with 96 per cent alcohol

EXPERIMENT 13 (patient J B) —To the incubated mixture of meat (250 Gm) and gastric juice concentrated alcohol was added until a concentration of 70 per

cent was reached The fluid was filtered, and the filtrate was concentrated in vacuo The concentrate was administered daily to the patient Again a therapeutic effect was absent

Comment—The absence of therapeutically active amounts of liver factor in the incubated mixture is still more clearly shown in this experiment The possibility that an active substance with other properties had been formed was investigated in the next experiment

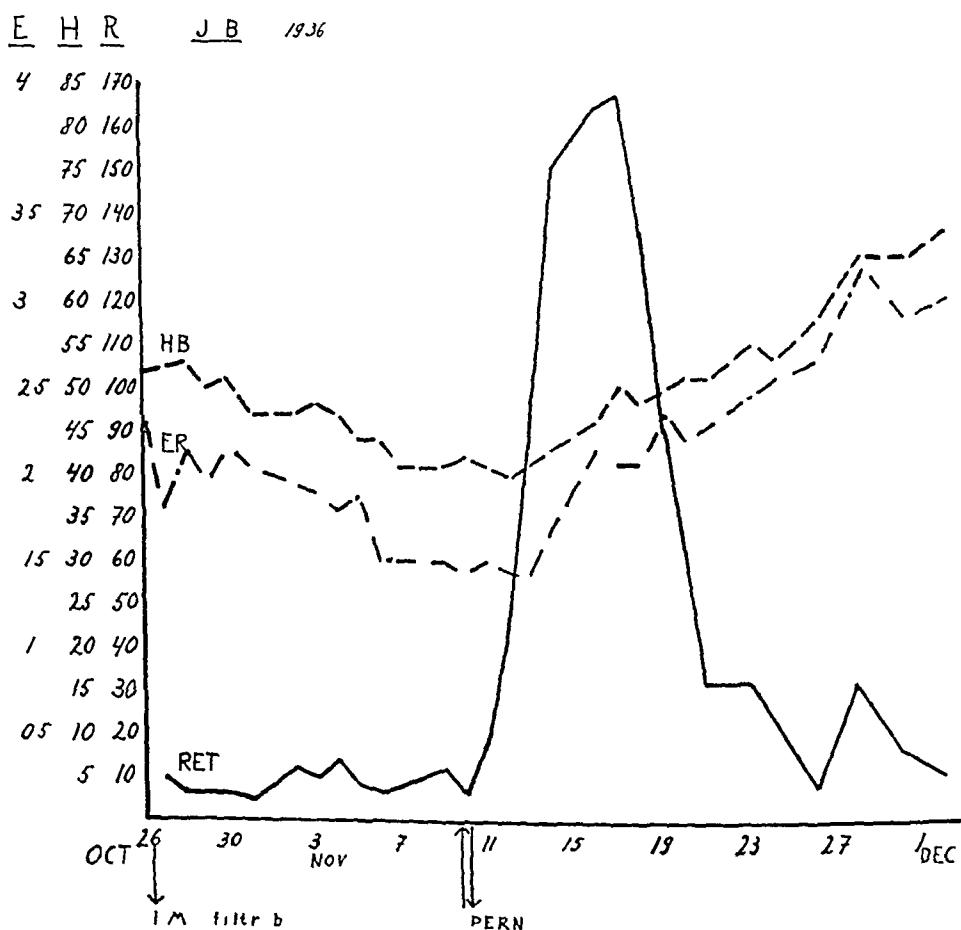


Chart 13 (experiment 13) —The incubated mixture of alcoholic extract of meat (250 Gm) and gastric juice was treated with 70 per cent alcohol The filtrate (indicated by the letters IM, filtr b) was given daily to the patient by mouth from Oct 10 to Nov 10, 1936 Pernaemon was injected daily from November 10

EXPERIMENT 14 (patient v B M) —To the incubated mixture of meat (250 Gm) and gastric juice concentrated alcohol was added until a concentration of 70 per cent was reached By filtration a filtrate (a) and a precipitate (b) were collected The filtrate, a, was concentrated in vacuo The precipitate, b, was dissolved in isotonic salt solution Then the filtrate, a, and the precipitate, b, were reunited, and the mixture, containing all the original substance, was administered to the patient Again a negative effect was observed

Comment—This experiment proves that the incubated mixture of meat and gastric juice, which is therapeutically active, is inactivated by treatment with 70 per cent alcohol and reunion of the two fractions. Inactivation of the incubated mixture by heating to 80 C for one-half hour has already been described by Castle. The in vitro formation of the antianemic liver principle cannot be accepted any longer. Taylor, Castle, Heinle and Adams⁶ demonstrated the proteolytic activity of

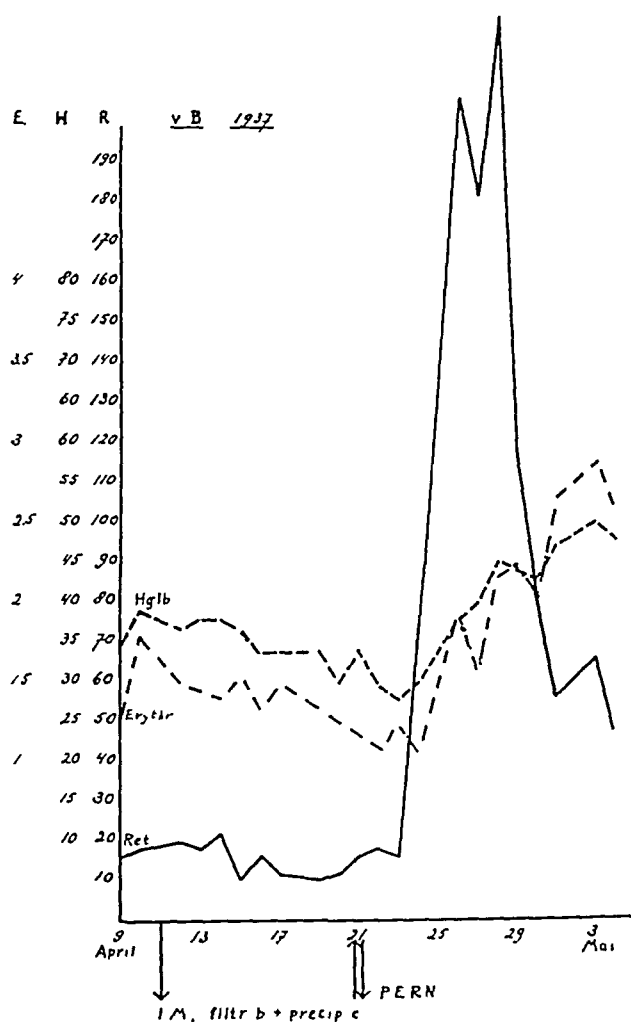
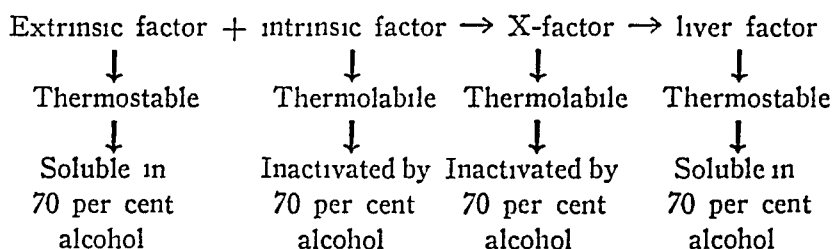


Chart 14 (experiment 14)—The incubated mixture of alcoholic extract of meat (250 Gm) and gastric juice was treated with 70 per cent alcohol. The reunited filtrate and precipitate (indicated by the letters I M, filtr *b* + precip *c*) was given daily to the patient by mouth from April 11 to 21, 1937. Pernaemon was injected daily from April 21.

neutralized gastric juice and the identical behavior of this ferment and the intrinsic factor in many respects. No conclusions are drawn from these experiments by the authors. However, it is evident that the actual identity of the newly found proteolytic ferment and the intrinsic factor is considered. The acceptance of this identity necessarily leads to the

conception of the formation of an intermediate factor (subsequently called X factor for convenience) This hypothesis can be expressed in the following manner



This sequence of events, although perhaps not impossible, is very improbable. It will be seen that the two properties known of the X factor, e g, inactivation by heating to 80 C and inactivation by treatment with 70 per cent alcohol, are also inherent to one of the constituents of the incubated mixture, e g, the intrinsic factor (for proof of the inactivation of intrinsic factor by 70 per cent alcohol, compare the following experiment [15], first period). These experiments suggest strongly the possibility that in the incubated mixture no X factor is formed *in vitro*. If this is true, only an *in vivo* interaction between the extrinsic and the intrinsic factor can be assumed.

The absence of an intermediate X factor formed by the fermentive splitting of the extrinsic factor was further demonstrated in the next experiment (second period).

EXPERIMENT 15 (patient J R)—In the first period, demonstration of the inactivation of the intrinsic factor in the gastric juice by 70 per cent alcohol was done. To 75 cc of gastric juice concentrated alcohol was added until a concentration of 70 per cent was reached. The mixture was filtered and the filtrate and precipitate were reunited in the manner previously described (experiment 14). The resulting fluid, containing all the substances originally present in the gastric juice, was mixed with alcoholic extract of meat (250 Gm) and administered to the patient. This patient had a constant high level of reticulocytes in his blood, but administration of the mixture had no effect on the reticulocytes, hemoglobin or erythrocytes.

In the second period, the mixture of alcoholic extract of meat (500 Gm) and 150 cc of gastric juice was incubated for four hours. Afterward, ultrafiltration of the incubated mixture through collodion membranes was carried out. The nonfiltrable rest (about one-third of the original volume) was diluted with water and again ultrafiltered. In this manner no more than one-ninth of the ultrafiltrable substances could remain in the nonultrafiltrable portion of the fluid.

The ultrafiltrates were administered daily to the patient. The result was negative.

In the third period, the alcoholic extract of meat (330 Gm) was first ultrafiltered. The small rest in the collodion sacs was diluted with physiologic solution of sodium chloride and again ultrafiltered. The first and second ultrafiltrates were mixed, and 75 cc of gastric juice was added. The mixture was administered daily to the patient. A marked reticulocyte crisis occurred, together with a fast increase of hemoglobin and erythrocytes.

Comment on Experiment 15—The first period shows clearly that treatment of the gastric juice with 70 per cent alcohol leads to inactivation of the intrinsic factor. This had already been shown in the first period of experiment 9, but this experiment was not so clearcut, owing to the nonspecific rise of the reticulocytes in the beginning of the experiment. It is possible that inactivation of gastric juice by 70 per cent alcohol is not complete.

In the second period the possible formation of an intermediate X substance by the enzymatic splitting of the extrinsic factor was investigated. The fact that the extrinsic factor passes through an ultrafilter was demonstrated in experiment 7 and was shown again in the third

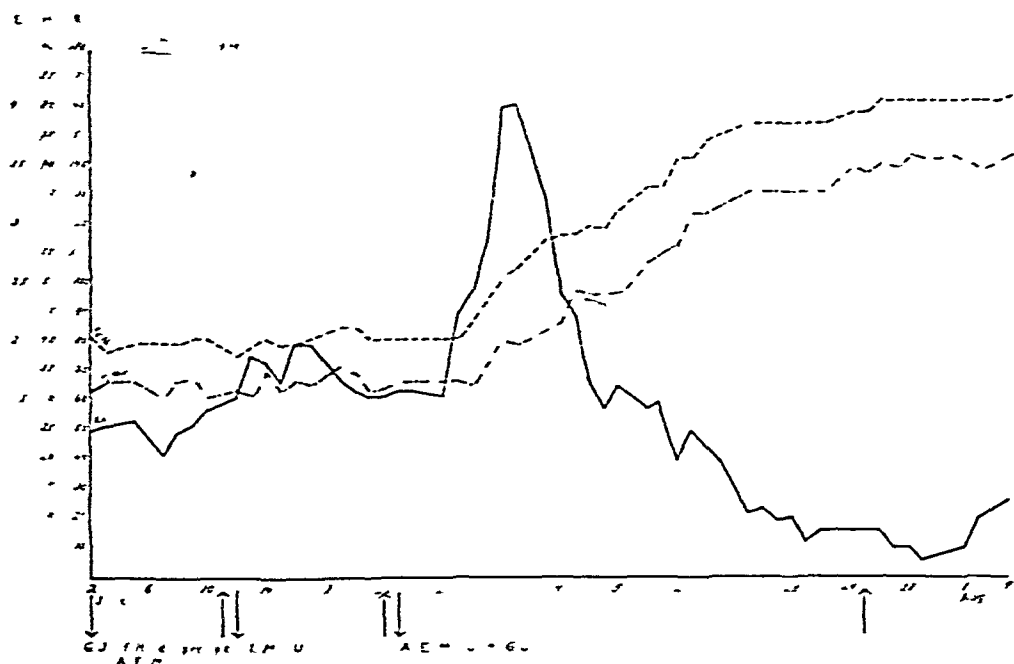


Chart 15 (experiment 15) —In the first period, gastric juice (75 cc.) was treated with 70 per cent alcohol. The reunited filtrate (*d*) and precipitate (*e*) were mixed with alcoholic extract of meat (250 Gm) and given daily to the patient by mouth from June 2 to 11, 1939. In the second period the incubated mixture of alcoholic extract of meat (500 Gm) and gastric juice (150 cc) was ultrafiltered. The ultrafiltrate (indicated by the letters I M U) was given daily to the patient by mouth from June 13 to 22. In the third period, the alcoholic extract of meat (330 Gm) was ultrafiltered. The ultrafiltrate (indicated by the letters A. E. M. U) was mixed with gastric juice (75 cc) and given daily to the patient by mouth from June 23 to July 25.

period of the present experiment. The products which can be formed by enzymatic splitting of the extrinsic factor must have still smaller molecules and must pass the ultrafilter even more easily than does the extrinsic factor. The second period of the present experiment shows clearly that these splitting products of the extrinsic factor cannot be demonstrated.

The third period shows that a much smaller amount of extrinsic factor, ultrafiltered *before* addition of the gastric juice, gives a marked therapeutic response. This positive result with the ultrafiltrate originating from $\frac{1}{3}$ Kg of meat contrasts with the insufficient response to the same amount of ultrafiltrate in experiment 7. This probably can be explained by the careful washing of the nonultrafiltrable rest and the ultrafilter in the present experiment, although individual quantitative differences in the therapeutic response to moderate amounts of effective mixtures cannot be excluded.

Comparison of the second and third periods of this experiment forms a strong argument against the hypothesis that an intermediate substance is formed by enzymatic splitting of the extrinsic factor. The possibility of insufficient formation of this hypothetic intermediate substance under the conditions of the experiment must be considered. This interpretation of the experiment is improbable because of the large amount of the original mixture (e g, the known effective amounts of both extrinsic and intrinsic factor were doubled) and because of the total absence of even a small reticulocyte response, which may indicate administration of a therapeutic substance in an insufficient amount.

It seems to me that so many arguments against the existence of the hypothetic intermediate X substance have been shown that burden for the clinical proof of this hypothesis now lies on the other side.

The possibility that the combined action of gastric juice and duodenal juice could lead to transformation of the extrinsic factor into the liver factor was considered in the next experiment.

EXPERIMENT 16 (patient J. D.)—The 90 per cent alcoholic extract of meat (250 Gm) was mixed with 50 cc of gastric juice and 50 cc of duodenal juice (obtained by duodenal tubage) and incubated for four hours. The incubated mixture was treated with 70 per cent alcohol, and the filtrate was administered daily to the patient by mouth for ten days, without any result. Afterward, injections of pernaemon gave a clearcut therapeutic result.

Comment on Experiment 16—The combined effect of gastric and duodenal juice on the extrinsic factor did not lead to formation of an active principle soluble in 70 per cent alcohol, e g, the liver factor. An analogous experiment has been performed by Castle, also with negative results.

The evidence of experiments 11 to 16 makes it probable that no reaction *in vitro* between the extrinsic factor and the intrinsic factor exists and that the essential interaction of these substances can take place only in the body. Castle has shown that a mixture of the extrinsic and the intrinsic factor is not active when the fraction of the mixture is strongly acid (p_H , 1.8 to 2.5), he concluded from this fact that the interaction between the extrinsic and the intrinsic factor probably takes

place in the gastrointestinal tract, because the inhibitive action of the acid reaction could not be maintained after absorption from the intestine. This fact, combined with the necessity of an *in vivo* phase for interaction of the extrinsic and the intrinsic factor, draws attention to the intestinal wall as the only possible place where these two conditions can be fulfilled. The experiments of Uotila⁷ on the antianemic activity of the intestinal mucosa and of a progressive activity in the lower parts of the ileum are of special interest in this connection. The mode of action

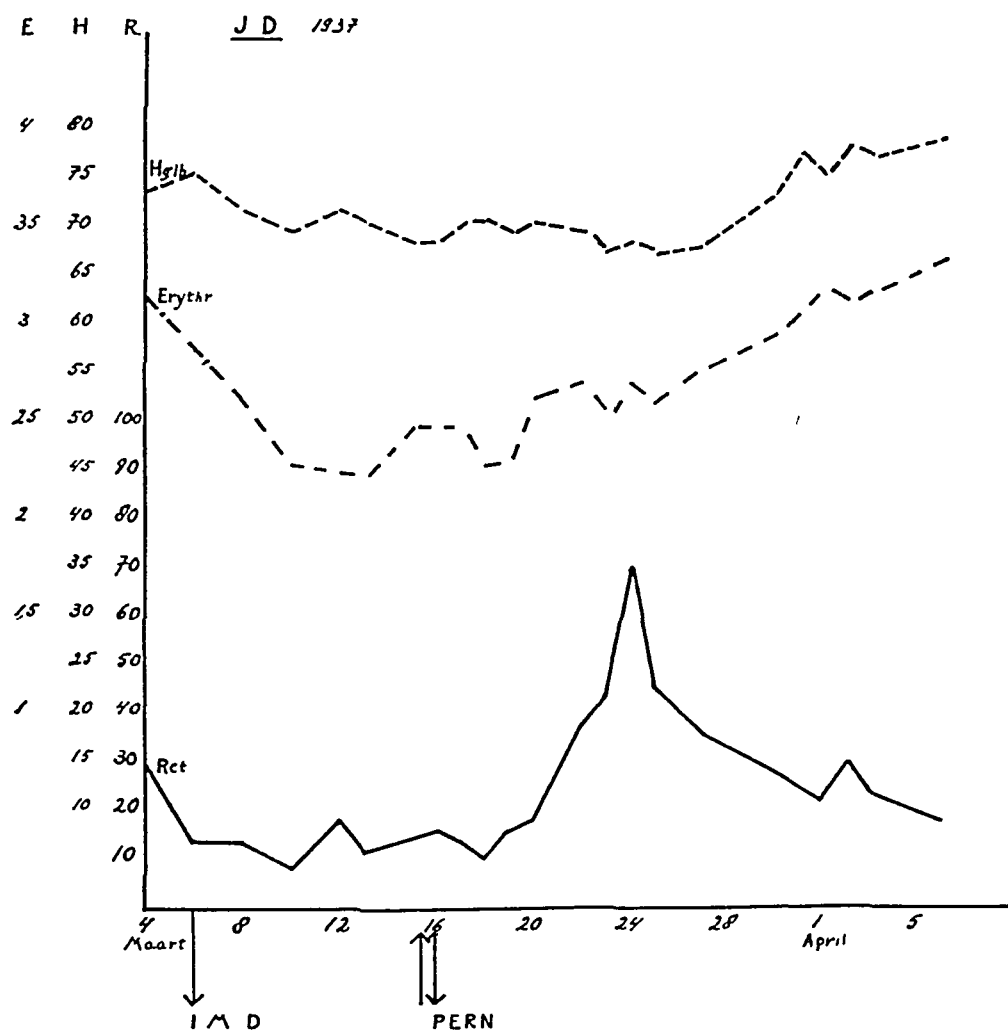


Chart 16 (experiment 16)—Incubated mixture of alcoholic extract of meat (250 Gm) and gastric juice (50 cc) was treated with 70 per cent alcohol (indicated by the letters IMD) and given daily to the patient from March 6 to 16, 1937. Pernaemon was injected daily from March 16.

of the intestinal wall in this reaction will have to be determined by later experiments.

Parenteral application of the extrinsic factor alone or in combination with gastric juice is now under investigation. Small quantities of different active fractions of the meat extract have been injected into healthy

⁷ Uotila, U. Acta med Scandinav 95 415, 1938

adults and into some patients with pernicious anemia, without effect on blood formation. Injection of greater quantities has been inhibited by severe local irritation, the separation of the irritating substance from the active principle is now being studied.

SUMMARY

A study of the properties of the extrinsic factor in meat has been made.

The extrinsic factor was present in a 70 to 80 per cent alcoholic extract of meat.

Fats and lipoids could be removed from this extract by ether extraction without loss of activity.

The extrinsic factor present in the extract passed through an ultra-filter.

A fraction of the extrinsic factor (less than 50 per cent) was present in the precipitate obtained by saturation of the extract with ammonium sulfate.

An analysis of Castle's reaction has been carried out.

The alleged formation of the antianemic liver factor in the incubated mixture of meat and gastric juice was investigated. The liver factor could not be demonstrated by treatment of the incubated mixture with 70 per cent alcohol and precipitation of the filtrate with 96 per cent alcohol, the precipitate was inactive when given by mouth or by injection.

Treatment of the incubated mixture with 70 per cent alcohol alone led to inactivation of the mixture.

Attention is drawn to the intestinal wall as the probable site of this reaction.

The conclusion is drawn that no reaction *in vitro* takes place between the extrinsic and the intrinsic factor and that only an *in vivo* reaction exists.

TRANSITORY INFILTRATION OF THE LUNG WITH EOSINOPHILIA

LOFFLER'S SYNDROME

R FREUND, M D

AND

S SAMUELSON, M D

JERUSALEM, PALESTINE

Since Löffler in 1931 first drew attention to a condition characterized by transitory infiltration of the lung and eosinophilia, increasing interest has been paid to this symptom complex by those engaged in the treatment of diseases of the lung. Löffler's syndrome consists of four cardinal signs which have been present in all the cases so far reported: signs of pulmonary disease on auscultation and percussion, the presence of a corresponding shadow in the roentgenogram, transience of the pulmonary signs and increase of the eosinophils in the blood.

One hundred and five cases have so far been reported, 51 by Löffler¹ himself. The importance of this condition, from the point of view of both differential diagnosis and prognosis, induces us to report a case which came under our observation.

The patient was a woman aged 25, of the asthenic type, 5 feet 8½ inches (174 cm) tall and weighing 126 pounds (57 Kg). After a long-drawn-out attack of bronchitis six years before, she had been subject to repeated attacks of catarrh of the air passages and bronchial asthma (particularly when the relative humidity was high or when she was in an atmosphere laden with tobacco smoke). No allergy of exogenic nature was demonstrable. Roentgen examination of the lungs on several occasions in recent years had shown them to be in normal condition. The blood picture and the sedimentation rate were normal. The heart and the circulatory system were normal. The blood pressure was 105 systolic and 80 diastolic (in the special climatic conditions of Palestine, which have a marked effect on the circulation, a single reading is of no great significance and cannot be compared to a like observation in Europe).

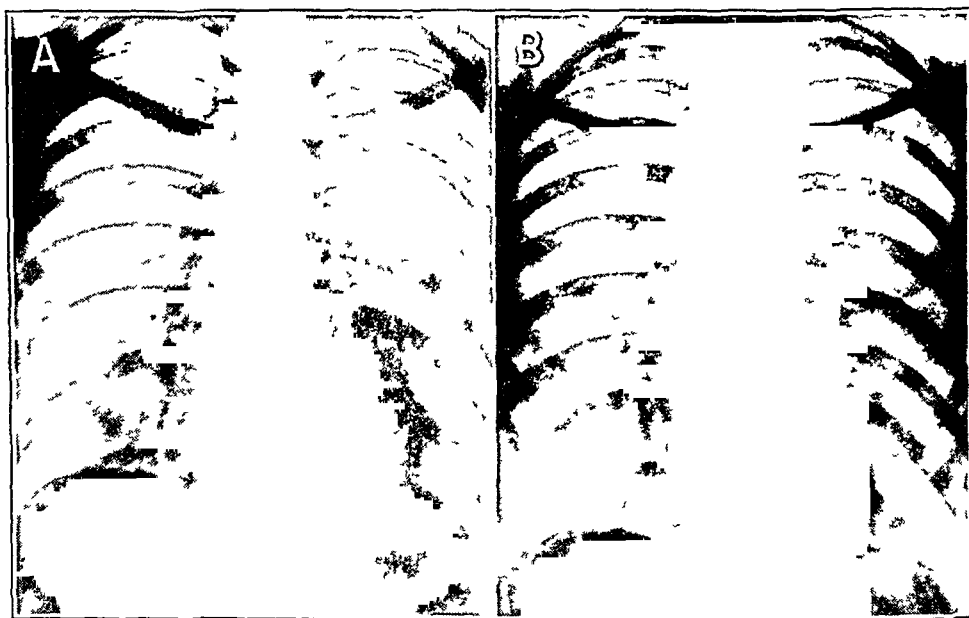
Nov 8, 1937 The patient felt ill. Her temperature (axillary) was 100 F. There was pain on the left side of the chest on coughing. Over the middle of the left clavicle there was a gland the size of a plum, fairly hard and painful to the touch, palpation brought about a fit of coughing. On the left side below the clavicle and in the corresponding area posteriorly an area was noted as large as the palm of the hand, with decreased resonance, diminished breath sounds and a

¹ Löffler, W. (a) Zur Differential-Diagnose der Lungeninfiltrationen II Ueber fluchtige Succedan-Infiltrate (mit Eosinophilie), Beitr z Klin d Tuberk **79** 368-382, 1932, (b) Die fluchtigen Lungeninfiltrate mit Eosinophilie, Schweiz med Wchnschr **66** 1069-1078 (Nov 7) 1936

few fine crepitations, surrounded by an area of bronchial breathing. There was no asthma. The cough was not productive. The clinical diagnosis was infiltration in the upper lobe of the left lung. The differential diagnosis was incipient phthisis (?).

November 9 The gland was the size of an almond but softer and still tender to touch. The temperature was normal. There was no change in the lung. Roentgen ray examination showed lateral to the left hilus a triangular shadow consisting of small patches which still enabled the structure of the lung to be made out. The diaphragm moved well. The phrenicocostal sinus was clear. The roentgen diagnosis was infiltration in the middle field of the left lung (fig A).

November 10 The condition was unchanged. The blood picture and sedimentation rate are given in table 1. The diagnosis was Löffler's syndrome.



Roentgenograms of patient with Löffler's syndrome. A (Nov 9), infiltration in the middle field of the left lobe. B (Nov 25), no sign of the infiltration.

November 11 There was no change in the pulmonary condition. The gland was no longer palpable, but there was slight pain on pressure. There was slight pain on the left side of the chest on deep inspiration and on coughing.

November 13 The pulmonary condition was still demonstrable. There was a dry cough.

November 14 to November 16 No change was noted.

November 17 Diffuse bronchitis developed overnight, affecting both lungs. There were moist rales. No rise in temperature took place. Roentgen examination showed no sign of infiltration apart from a small area in the lateral part of the left middle field. The diagnosis of Löffler's syndrome was confirmed.

November 19 The bronchitis was disappearing. There was clear, gelatinous, tenacious sputum, containing few cells, no eosinophils, no red cells and no helminth eggs.

November 22 In the lungs no abnormalities were noted. The patient felt well and resumed her office work.

November 25 On roentgen examination there was no sign of infiltration of the left upper lobe (fig B)

Table 1 gives the results of examinations of the blood during the period under observation. Examination of the stools on several occasions failed to reveal the presence of either worms or eggs.

The findings and the course of the disease—the mild symptoms and the marked objective appearances, the shadows in the roentgenogram of the lung, the transitory nature of the pulmonary condition and the eosinophilia—led us to conclude that we were dealing with a case of Löffler's syndrome.

A statistical survey of the cases hitherto reported in the literature is given in table 2.

It is to be regretted that detailed information is provided in only a quarter of the total number of cases reported. It would be desirable

TABLE 1—Results of Examination of the Blood

Date	Red Blood Cells per Cu Mm	Hemo- globin, %	White Cells per Cu Mm	Baso- phils, %	Eosino- phils, %	Neutrophils		Lym- pho- cytes, %	Mono- cytes, %	Sedi- menta- tion Rate, Mm
						Band Form, %	Seg- mented, %			
11/10	3,800,000	70	9,850	1	11	3	55	27	3	16
11/11				0	22	4	43	26	5	
11/13			10,500	0	12	3	65	15	5	
11/14			9,575	0	18	4	50	23	5	
11/15			8,925	1	20	2	56	19	2	
11/16	4,620,000	80	9,950	0	18	2.5	52.5	22	5	9
11/17			14,800	0	18	2.5	65.5	11.5	2.5	
11/19				1.5	21	3	43.5	29	2	
11/24			6,675	0	12	0	45	38	5	
11/27			8,300	1	8.5	0	51	31	8.5	

from the point of view of systematic study were physicians to follow a scheme in taking histories which would provide information on (1) age, (2) sex, (3) season and climate, (4) site of disease, (5) symptoms, (6) clinical signs, (7) roentgen observations, (8) blood picture, (9) sputum and stool, (10) duration of the disease and (11) possible etiologic factors. Such histories would make clinical classification possible.

It is not surprising that this condition was not defined earlier, for it is only in the last decade, when for social and hygienic reasons large numbers of examinations have been made in outpatient departments and clinics, that it has been possible to carry out observations which enabled Löffler to define this syndrome as a pathologic entity. The condition is usually so mild that the patient is rarely driven to consult a doctor. The signs, however, are so alarming, from the point of view of differential diagnosis and therapeutic measures undertaken, and so uniformly clear and sharply defined, that Löffler's syndrome has taken its place in the field of special pathology.

The absence of anatomic or histologic observations which might throw a light on the pathologic process is due to the fact that in all the cases hitherto observed the condition has ended in resolution

TABLE 2—*Summary of Cases of Löffler's Syndrome Reported in the Literature*

Author	Number of Cases	Sex		Age		Site of Infiltration			Supposed Cause	Country, Season	Comment
		M	F	Adults	Children	Right	Left	Both			
Löffler ¹	51	34	17	51		8	1	2	Tuberculous (all)	Switzerland, July, Aug	Outpatients, 1931-1936
Geiger ^{11a}	15			6	9				Undecided, 9 patients exposed to tuberculosis	Switzerland, May-Aug	Tuberculosis dispensary, routine examinations 1933-1936
Oeri ^{11b}	5			5					Concidental tuberculosis	Switzerland, spring	Basel, sanatorium, 120 beds
Wild ⁶	14			—	14				Not stated, ascariasis on 4 occasions	Switzerland, June-Aug	Routine examinations in 2 elementary school classes
Jeanneret et Fame ^{11c}	3			3		3			?	Switzerland, ?	
Steiger and Rohner ²	1	1		1			1		Allergy	Switzerland, March	Personal observation (H. R.) 1936
Hansson ⁸	1		1	1				1	Allergy	Sweden, May-Aug	Relapse in bronchial asthma, 1933, 1934
Rosset and Houriet ⁹	2	1	1	2		2		(2)	Allergy	Switzerland, June, July	Both began on right side, then also left side, 1937
Leitner ^{11d}	8			8		7	1		?	Switzerland, winter	Davos, sanatorium, 120 beds
Cohen ^{11e}	1			1					Allergy	France, summer	Migraine patient
Viersma ¹⁰	2	1	1	2		1	1		?	Holland, April, July	
Freund and Samuelson	1		1	1			1		Allergy ?	Palestine, autumn	Relapse of bronchitis and bronchial asthma, 1937

As for etiologic factors, there is little divergence of opinion among observers. Steiger and Rohner ² and Engel ³ differed from the majority

² Steiger, J, and Rohner, H. Fluchtige Lungeninfiltrierungen mit Eosinophilie, Deutsches Tuberk.-Bl. **11** 154-158 (June) 1937, in discussion on Löffler ^{1b}

³ Engel, D. Anaphylaktisches Frühjahrsodem der Lunge. Eine pseudo-epidemische Erkrankung, Med. Klin. **2** 1466 (Nov. 8) 1935, Ueber eine eigenartige anaphylaktische Erkrankung der Lunge, Beitr. z. Klin. d. Tuberk. **87** 239-250, 1935

in speaking of an "epidemic incidence", but as there is no foundation for this belief from an epidemiologic point of view, the statement may be ignored. Engel in China and Koino⁴ in Japan stated the belief that they could trace a direct connection with external factors. Engel observed a series of cases during the season when the privet was in blossom and regarded the condition as an anaphylactic reaction caused by breathing privet pollen. No such specific connection was established in Europe.

It may here be mentioned that Dickson⁵ has recently described the coccidiomycosis syndrome, with details of its pathogenesis. He described the clinical and roentgen appearance of the lung in the acute stage, and this is identical with that of Löffler's syndrome. It seems probable that the observations of Engel, Koino and Dickson represent similar reactions to different antigens.

In this connection, some theoretic interest attaches to the experimental observations of Koino on the relation between the wanderings of ascaris larvae in the human body and the occurrence of pneumonia. But we agree with Löffler that under natural conditions when the infection is not as massive as it was in Koino's personal experiment, milder conditions may appear which may well fall into our category. Wild's⁶ observations support this, he alone among all other observers found ascariasis in 4 of a total of 14 cases reported (table 2).

Wieland's⁷ suggestion that climatic influences should be borne in mind is worth noting, he stated the opinion that indiscreet and prolonged exposure to the sun may lead to transient congestive conditions in particular areas of the lung. But in our opinion that plays only an exciting and not an etiologic role.

All writers, however, who have dealt with the etiology of Löffler's syndrome are agreed that allergic phenomena play a decisive part in its pathogenesis. Löffler himself, who has made the fullest study of the largest series of cases investigated and regarded the "transitory infiltration with eosinophilia" as a microbid or frequently as a tuberculid, based his opinions on the original classic conception of allergy in its narrower sense. Whether the preponderating amount of material on tuberculosis discussed by Swiss writers has not tended to affect the figures will be decided when the results of observation in other countries are known. In the present state of knowledge one should avoid analyzing the etiologic factors of each reported case and refer to the

4 Koino, S. Japan M. World **2** 11, 1922, cited by Löffler^{1b}

5 Dickson, E. C. Coccidiomycosis, J. A. M. A **111** 1362-1365 (Oct. 8) 1938

6 Wild, in discussion on Löffler^{1b}

7 Wieland, E., in discussion on Löffler^{1b}

details given in the original published observations (Löffler, Steiger and Rohner, Hansson,⁸ Rossel and Houriet,⁹ Viersma¹⁰ and others¹¹)

In all cases hitherto reported the condition has run such a mild course that the question of specific therapy has not arisen

It is our opinion that Löffler's syndrome is a clinical entity the definition of which is particularly important from the point of view of prognosis and treatment. We believe, with Rossel and Houriet, that we are dealing with a condition in which a variety of causative factors may produce this clearly defined symptom complex in a suitable case.

There appears to be no doubt that the clinical observations in the lung which indicate infiltration, whether cellular, exudative or atelectatic (as in our case), can always be established by careful percussion and auscultation. This should be an indication—independent of the course and intensity of the condition—for examination of the blood (leukocyte count and blood film, on a thick drop for a rough estimate of eosinophils) and roentgen examination. The diagnosis of this symptom complex is of more than mere academic interest, mild as its course and results are. Its recognition is of the utmost practical importance from the point of view of differential diagnosis from pulmonary tuberculosis, as may be noted in the case reported by Dickson, in which a mistaken diagnosis of tuberculosis was made, with all its attendant consequences.

SUMMARY

Observations are made on Löffler's syndrome, and a further case is reported.

The importance of the recognition of Löffler's syndrome lies in its differential diagnosis from tuberculosis, for it is characterized by similar clinical observations and roentgenologic appearance of the lungs.

Examination of the blood which reveals eosinophilia points to the possibility of a "transitory infiltration of the lung with eosinophilia" (Löffler's syndrome). Further clinical and roentgenologic observation confirms this and differentiates the condition from tuberculosis.

8 Hansson, N. Transitory Lung Infiltration with Eosinophilia, *Acta radiol* **18** 207-212, 1937.

9 Rossel, G., and Houriet, J. H. Infiltrations pulmonaires fugaces successives avec eosinophilie sanguine, *J med de Leysin* **15** 245 (Nov-Dec) 1937.

10 Viersma, H. J. The Syndrome of Löffler, *Nederl tijdschr v geneesk* **82** 5372-5380 (Nov 5) 1938.

11 (a) Geiger, H., in discussion on Löffler^{1b} (b) Oeri, in discussion on Löffler^{1b} (c) Jeanneret, R., and Fame, F. À propos des "ombres radiologiques fugaces," *J med de Leysin* **13** 819-832 (July-Aug) 1934. (d) Leitner, J. Ueber flüchtige hyperergische Lungeninfiltrate mit Eosinophilie bei Tuberkulose, *Beitr z Klin d Tuberk* **88** 388-420, 1936. (e) Cohen, R. Le syndrome de Löffler, *Presse med* **46** 797-799 (May 18) 1938.

SUBACUTE COR PULMONALE

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Admitting the rarity of occurrence, Brill and Robertson¹ called attention to what may prove to constitute a clinicopathologic entity, namely, subacute cor pulmonale. The features of this condition, according to their case report and to 2 similar ones that they were able to find in the literature, differ rather sharply from those of the acute and chronic forms of cor pulmonale. The acute form, confined practically to pulmonary embolism, is rarely associated with right ventricular hypertrophy. The chronic primary type² includes pulmonary stenosis and insufficiency, pulmonary endarteritis, organic tricuspid insufficiency, mitral stenosis, diffuse pulmonary fibrosis³ and pulmonary emphysema. In the latter group the clinical course is usually protracted, right ventricular hypertrophy and dilatation are usually marked, and the cause is often clinically apparent. The subacute variety is characterized by a fairly rapid (nine days to two months) development and termination of signs and symptoms of strain of the right side of the heart in persons giving no history of previous cardiac or pulmonary disease, by moderate enlargement and dilatation of the right side of the heart and, further, by being undiagnosed.

In the case presented by Brill and Robertson and in the 2 abstracted by them (Krutzsch⁴ and Schmidt⁵) the right ventricular strain was due to carcinomatous metastases to the pulmonary arterioles and to the peribronchial lymphatics, with secondary arteriolar thromboses. The

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1 Brill, I. C., and Robertson, T. D. Subacute Cor Pulmonale, *Arch. Int. Med.* **60**: 1043-1057 (Dec.) 1937.

2 Thompson, W. P., and White, P. D. The Commonest Cause of Hypertrophy of the Right Ventricle—Left Ventricular Strain and Failure, *Am. Heart J.* **12**: 641-649 (Dec.) 1936.

3 Coggin, C. B., Griggs, D. E., and Stilson, W. L. The Heart in Pneumoconiosis, *Am. Heart J.* **16**: 411-421 (Oct.) 1938. Thompson and White²

4 Krutzsch, G. Ueber rechtsseitige Herzhypertrophie durch Einengung des Gesamtquerschnittes der kleineren und kleinsten Lungenarterien, *Frankfurt. Ztschr. f. Path.* **23**: 247-271, 1920.

5 Schmidt, M. B. Die Verbreitungswege der Karzinome und die Beziehung generalisierter Sarkome zu den leukamischen Neubildungen, *Jena, Gustav Fischer*, 1903.

primary tumors in all instances were unrecognized gastric carcinomas. In 2 of these cases diffuse ramifying white threads representing tumor were seen macroscopically coursing through the exposed surfaces of the lungs. No such observations were noted in the third instance. Adequate clinical explanation of the cor pulmonale was lacking in all 3.

The following case presents a condition that clinically and pathologically readily fits that recently designated as subacute cor pulmonale. The only differing point in this instance is that the primary carcinoma arose in the breast rather than in the stomach.

REPORT OF A CASE

History—Mrs J N, a white woman aged 65, entered St Luke's Hospital on Jan 21, 1939 complaining chiefly of shortness of breath. Nineteen months prior to this hospitalization she had had a radical amputation of her right breast because of carcinoma. This operation was performed elsewhere. One month after this procedure she stated that she first noticed "neuritis" in her left leg. Mild intermittent pain was noted occasionally to the time of admission. Otherwise her health had been good until three weeks previously, when she first noticed shortness of breath which was not brought on by exertion. Since that time this symptom had been severe and constant. She had had no cough or pain in the chest. There was no history of tuberculosis or pneumonia.

Course—Her temperature was 36.9 C (98.4 F) and her pulse rate 110 per minute. The systolic blood pressure was 140 mm of mercury and the diastolic 80 mm. The elongated radical mastectomy scar on the right side appeared well healed, and there was no evidence of recurrent tumor. There was no cyanosis. Examination of the chest gave essentially negative results, though a few fine rales were heard over the base of the right lung. The heart rate was fast (110) but regular. No cardiac murmurs were heard. The abdomen and extremities were essentially normal. The urine was normal. Examination of the blood showed moderate anemia: 3,870,000 red cells per cubic millimeter and 11 Gm of hemoglobin per hundred cubic centimeters. There were 79 per cent polymorphonuclear leukocytes, 15 per cent lymphocytes, 5 per cent monocytes and 1 per cent basophils. The Kolmer and Kline tests of the blood gave negative results. At this time it was felt that the patient had an intrathoracic metastatic carcinoma, although there were no clinical signs indicative of such a diagnosis. Shortly after entry a roentgenogram of the chest, read by Dr C C Fulmer, showed the heart to be of borderline size, with a full right margin (fig 1). The aortic arch was normal. Diffuse peribronchial thickening and some little evidence of emphysema were noted. Calcification was observed in both hilar zones. There was no roentgenologic evidence of metastatic tumor in the chest. A roentgenogram of the spine and pelvis prior to hospitalization showed no metastases. In spite of the patient's dyspnea she was fairly comfortable during the next few days. Her temperature remained within normal limits, and her respiratory rate was from 22 to 24 per minute. The pulse rate remained consistently elevated, ranging from 100 to 130 per minute. On the sixth day in the hospital (twenty-seven days after the onset of symptoms) her moderate dyspnea suddenly became severe, and she complained of pain in the left

side of the chest. She had no cyanosis. It was felt that she probably had a coronary occlusion. At this time her red blood cells numbered 4,430,000 per cubic millimeter. The hemoglobin amounted to 13.3 Gm per hundred cubic centimeters. The white blood cells numbered 13,300 per cubic millimeter. The differential count showed 77 per cent polymorphonuclear cells, 17 per cent lymphocytes and 6 per cent monocytes. She died before an electrocardiogram could be taken.

Gross Observations at Necropsy—The external examination of the body showed no abnormalities other than a slight symmetric increase in the anterior-posterior diameter of the chest, there was no dependent edema and no evidence of recurrent



Fig 1—Roentgenogram of the chest, showing the configuration of the heart (three days before death)

or metastatic tumor. The general nutrition of the body appeared fairly good. Aside from a few isolated, discrete metastatic carcinomatous nodules in the under surface of the left lobe of the liver (weight 1,310 Gm), there were no noteworthy changes in the abdominal organs or tissues. There was no evidence of a nutmeg condition of the liver. Both pleural spaces were obliterated by diffuse fibrous adhesions, but there was no evidence of tumor. These adhesions were separated with ease. Sagittal sections of each lung revealed fluffy, pinkish gray, air-containing presenting surfaces in which consolidation and tumor were not recognized. The right lung weighed 370 Gm and the left 290 Gm. The maximum transverse diameter of the heart measured 13 cm. Eleven centimeters of this anterior presenting surface was formed by the right ventricle and auricle, the former chamber

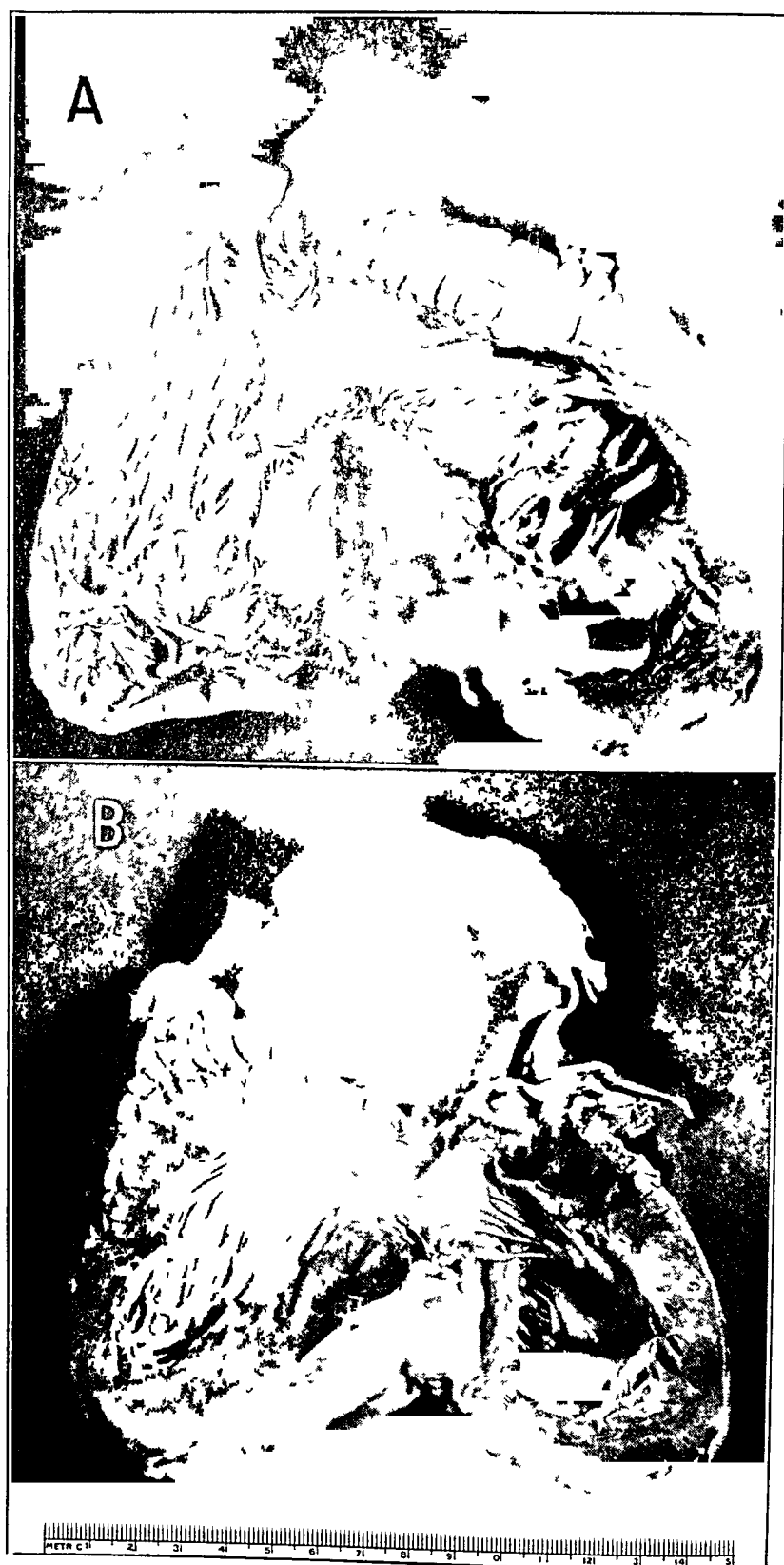


Fig 2—The heart, showing (A) the hypertrophy and dilatation of the right ventricle and (B) the smallness of the left ventricle and its trabeculae carneae

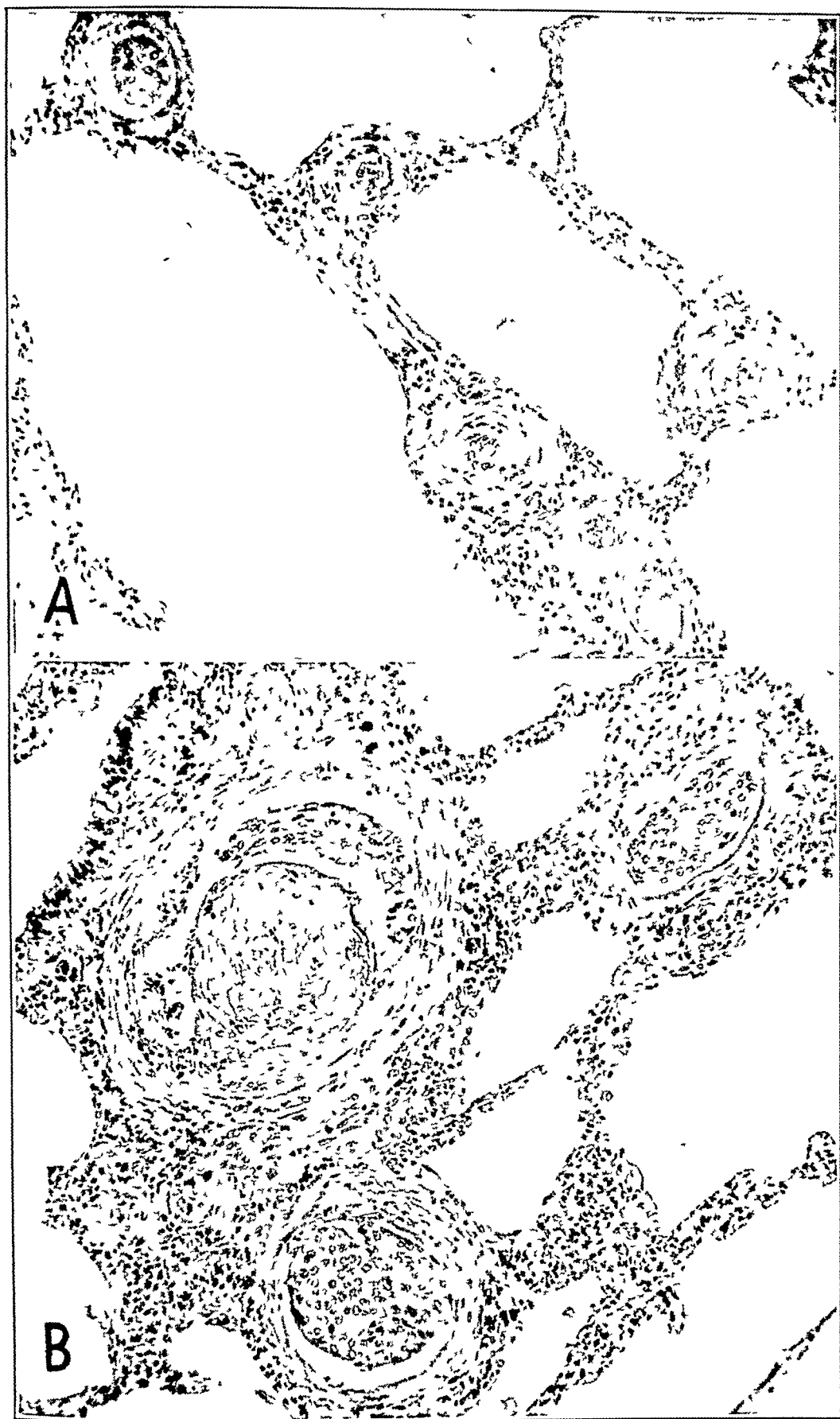


Fig 3—*A*, emboli of tumor cells in the dilated arterioles ($\times 117$) *B*, carcinoma cell plugging of prearteriolar pulmonary arteries, with secondary thrombosis ($\times 117$)

constituting a predominant share. The pulmonary conus bulged perceptibly. In contradistinction to the small left ventricle, the right was dilated and hypertrophied (fig 2). Thickening of the trabeculae carneae and of the papillary muscles was evident, and the former structures were flattened against the right ventricular wall. The myocardium of this chamber measured 6 mm in thickness at the base and from 3 to 4 mm at the apex. The wall of the left ventricle was 1.5 cm in thickness at the base and 1 cm at the apex. The trabeculae carneae

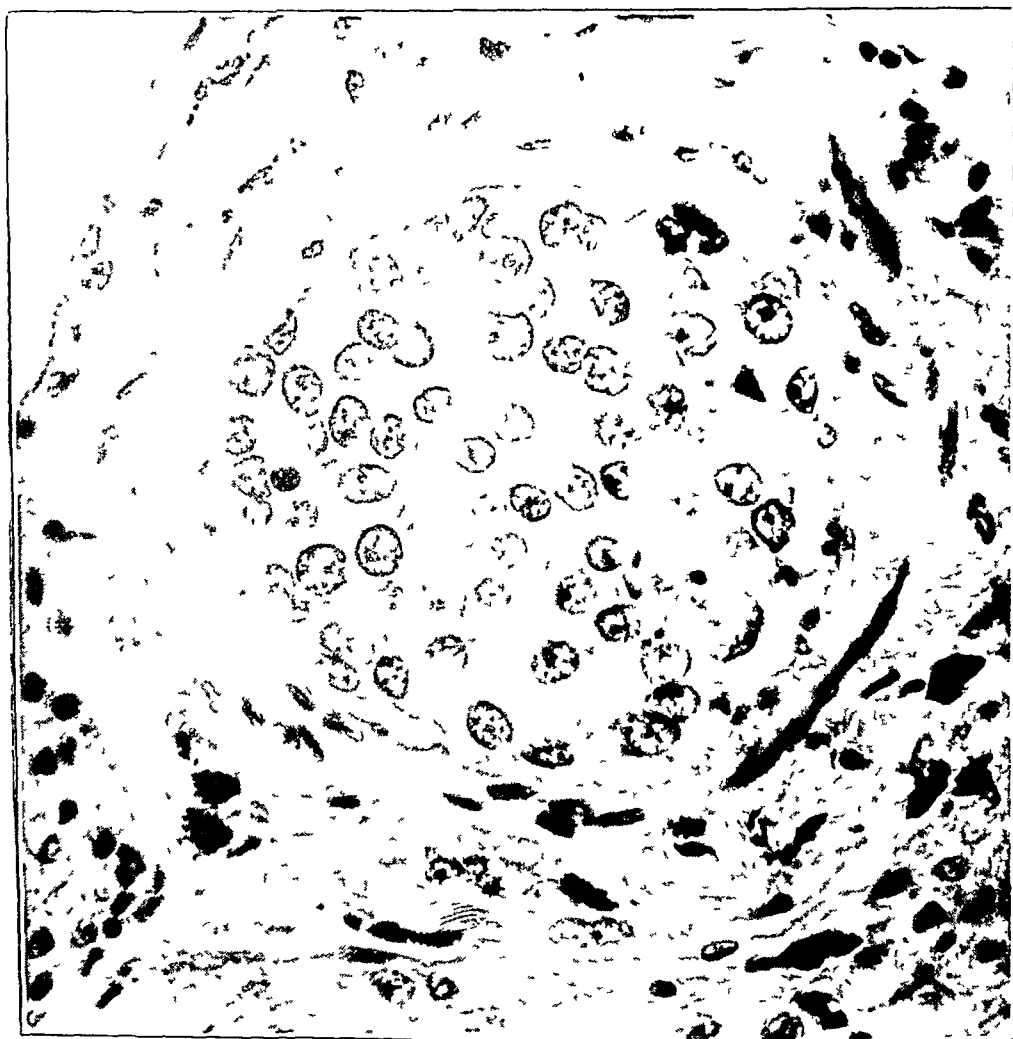


Fig 4—The carcinoma cells. Particles of coal dust lie in the perivascular lymphatics ($\times 479$)

here were much smaller than those on the right side of the heart. The cardiac valve rings measured as follows: pulmonic, 7 cm, aortic, 7 cm, mitral, 9 cm, and tricuspid, 12.5 cm. There was no evidence of valvular disease or of coronary arteriosclerosis or occlusion. The pulmonary arteries, aorta and cardiac septums were essentially normal. The heart weighed 325 Gm. During the removal of the brain the frontal bone was found to cut with decreased resistance and to be soft and porous. It measured 1.3 cm in thickness. The meninges were normal. There was no evidence of edema or tumor in the brain or brain stem. The organs

of the neck, the spinal medulla and the vertebral column were not examined. The cause of death was attributed to the cor pulmonale, which in itself was unexplained until the microscopic sections were seen.

Microscopic Observations at Necropsy—Microscopic sections of the lungs revealed the small divisions of the pulmonary arteries and the arterioles to contain solid nests of tumor cells (fig 3), which in most instances completely filled and plugged the vessel lumens. In certain of the vessels part of the lumen contained thrombi in addition to the carcinoma cells (fig 3B). A few such clots were old and organized. None of the vessels exhibited any evidence of intimal thickening. The individual tumor cells (fig 4) were closely packed and diffuse in arrangement and possessed rather large, round to oval, vesicular, slightly hyperchromatic nuclei. Nucleoli were prominent. Rare mitotic figures were present. These cells showed no evidence of invading the encircling walls of the blood vessels and were never seen in the capillaries, peribronchial lymphatics or lung tissue proper. Atrophy, with occasional rupture of an alveolar wall, was noted to a slight extent. Decalcified sections of the frontal bone revealed small nests of carcinoma cells present in young fibrous connective tissue stroma existing between degenerating bone trabeculae. These cells were identical to those present in the pulmonary arterioles and arteries.

Sections of the hypertrophic right ventricle revealed some moderate broadening of individual myocardial cells, with some squaring and hyperchromatism of the contained nuclei.

Anatomicopathologic Diagnoses—Pertinent diagnoses were (1) hypertrophy and dilatation of the right ventricle (subacute cor pulmonale), (2) embolism of the pulmonary arterioles and small arteries by tumor cells, with recent and organized thrombosis, (3) old (nineteen months) radical mastectomy on the right side, for carcinoma, (4) secondary carcinoma of the liver and frontal bone, and (5) slight pulmonary emphysema.

COMMENT

The only other reference in the literature to the term subacute cor pulmonale is one by Maddox,⁶ who, apparently unaware of Brill and Robertson's previous report, presented 2 clinical cases that he chose to classify under this title. The salient features of these cases are as follows:

A 42 year old woman with a history of long-standing hypertension was hospitalized with the complaints of pain in the chest (nine days), cough and cyanotic lips and fingers (five days). These symptoms and signs were such as to warrant an entry diagnosis of spontaneous pneumothorax. With the taking of digitalis she improved, and within eight days the roentgenographic transverse diameter of her heart changed from 14.4 cm to 12 cm. During this hospitalization her blood pressure ranged between 180 and 150 systolic and 110 to 90 diastolic.

The second patient was a 49 year old man who had complained of asthma for many years, expectorant cough (six years), edema of the ankles (three weeks),

⁶ Maddox, K. Subacute Cor Pulmonale, M. J. Australia **1** 18-21 (Jan 7) 1939.

dyspnea on exertion and cyanosis on hospitalization. His blood pressure was 180 systolic and 110 diastolic. The roentgenologic transverse diameter of his heart changed from 15.7 cm. on the fifth day in the hospital to 13.1 cm. two weeks later. After five weeks his cyanosis cleared, but the dyspnea remained.

If the criteria for the classification of subacute cor pulmonale are adhered to,¹ it is evident that Maddox' cases are of a different condition. Judging from his report it seems that they probably represent subacute bouts of right ventricular strain as a phase (initial?) of what may prove to be chronic cor pulmonale, secondary to a failing left ventricle in the hypertensive case and primary in the case of emphysema. Both of the patients had an antecedent history of cardiopulmonary disease, and both recovered.

Death in the case that I presented was due to failure of the right side of the heart, secondary to obstruction and obliteration of the finer pulmonary vascular bed, which in turn was due to embolism of the blood stream by carcinoma cells. The hypertrophy and dilatation of the right ventricle were not recognized clinically, and their cause was not understood at autopsy. After the examination of the microscopic sections of the lungs, the gross specimens were looked over more carefully. Then one was able to see a few pinhead-sized white dots throughout the lungs. They were always at least 2 or 3 cm. from one another. These visible lesions represented tumor cell emboli in the smaller pulmonary arteries. The emboli in the arterioles were not visible. The metastasis in the frontal bone and the few nodules in the liver were incidental in relation to the cause of death. In view of the moderate but definite right ventricular hypertrophy, as well as occasional well organized thrombi in certain of the arterioles, it appeared likely that pulmonary obstruction and hypertension existed before the onset of the patient's symptoms, twenty-seven days before death. The right side of the heart, in spite of the existence of dyspnea for this time and the progressive increase of the vascular obstruction, must have compensated to a moderate degree until near the end, as the liver at autopsy showed no gross or microscopic evidence of injury.

This case makes only the fourth published case of subacute cor pulmonale. In all instances the patients have been free of antecedent signs or symptoms of cardiorespiratory disease. The clinical course from the onset of symptoms to the time of death has varied from nine days to two months. The obstruction to the right side of the heart was due to embolism of the pulmonary arterioles by tumor cells, to metastases to the perivascular lymphatics or to both, with secondary thromboses. In 3 cases the primary carcinoma was in the stomach, and in another it

was located in the breast. It is thought that this condition is more common than it has so far proved to be, but the question of frequency awaits further reported examples.

SUMMARY

An example of an instance of subacute cor pulmonale is presented. Death was due to fairly rapid obstruction (clinically recognized twenty-seven days) of the pulmonary arterioles and prearteriolar arteries, with ensuing failure of the right side of the heart. The vascular obstruction was due to emboli of small carcinoma cells arising from a primary carcinoma of the breast, for which radical mastectomy had been performed nineteen months previously.

STUDIES OF THE BLOOD IN CONGESTIVE HEART FAILURE

WITH PARTICULAR REFERENCE TO RETICULOCYTOSIS, ERYTHROCYTE
FRAGILITY, BILIRUBINEMIA, UROBILINOGEN EXCRETION
AND CHANGES IN BLOOD VOLUME

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That the total circulating blood volume is increased during congestive heart failure¹ and is decreased after recovery^{1b c} has been convincingly demonstrated. Knowledge is incomplete, however, in regard to the mechanisms involved in creating and in disposing of the increased circulating volume of erythrocytes and plasma during the different stages of congestive failure. In the present investigation the reticulocyte percentage, red cell fragility, serum bilirubin and urinary and fecal excretion of pigment were studied in a series of patients at intervals during the height of, and recovery from, congestive heart failure, these findings were related to the observed changes in blood volume and clinical status.

METHODS

The total blood volume, plasma and circulating red blood cell mass were ascertained by means of Evans blue dye and the photoelectric colorimeter, as described by Gibson and Evans² and Gibson and Evelyn³. Measurements were

The study was aided in part by a grant from the Proctor Fund of Harvard Medical School.

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1 (a) Rowntree, L G, and Brown, G E. *The Volume of the Blood and Plasma in Health and Disease*, Philadelphia, W B Saunders Company, 1929. (b) Schurmeyer, A. *Ueber Blutmengenbestimmungen bei Herzfehlern*, Verhandl d deutsch Gesellsch f inn Med **40** 388, 1928, (c) Gibson, J G, and Evans, W A. *Clinical Studies of the Blood Volume. III Changes in Blood Volume, Venous Pressure and Blood Velocity Rate in Chronic Congestive Heart Failure*, J Clin Investigation **16** 851, 1937.

made soon after the patient's admission to the hospital and subsequently at four or eight day intervals (tables 1, 2, 3, 4 and 5) when he was in the fasting state. All blood samples were drawn, without stasis, from a cubital vein. Hematocrit measurements were made in Rourke-Ernstene sedimentation tubes⁴ with a mixture of potassium and ammonium oxalate as the anticoagulant. The total red cell mass was calculated from the average of three hematocrit measurements, taken at the beginning, in the middle and at the end of the plasma volume estimation. The initial reading was recorded on the charts and tables, whereas the average value, which was lower by from 10 to 30 per cent of cells, was used in the calculation of the total blood volume. The fragility of the red cells to hypotonic solutions of sodium chloride⁵ was observed immediately after withdrawal of the samples of blood. This procedure utilizes a constant volume of sample and volume of solution of sodium chloride, and each experiment was done at the same temperatures and intervals. The blood was collected without stasis and with a constant concentration of anticoagulant. All readings were made by the same observer.

The venous pressure⁶ and the quantity of bilirubin in the serum, as measured by the photoelectric colorimeter,⁷ were estimated at the time of the measurement of blood volume. The arm to tongue circulation time was measured with either sodium dehydrocholate or calcium gluconate, the same substance was used in all tests on any given patient.

The urinary and fecal biliary pigments were estimated by the method of Watson,⁸ in which all urobilin is reduced to urobilinogen and measured colorimetrically. Twenty-four hour collections of stools and urines were made separately each morning at 7 a. m. The urobilinogen content of the urine was measured immediately. The stools were kept in waxed cardboard containers in the refrigerator. Every fourth day, except for a longer or shorter period as indicated on the tables, the stools of the previous four days were weighed and thoroughly mixed and two accurately weighed samples taken for analysis. The values of the two samples agreed within plus or minus 10 per cent of their average when the fecal excretion was over approximately 75 mg of urobilinogen per day, and within plus

2 Gibson, J. G., and Evans, W. A. Clinical Studies of the Blood Volume. I. Clinical Application of a Method Employing the Azo Dye "Evans Blue" and the Spectro-Photometer, *J. Clin. Investigation* **16** 301, 1937.

3 Gibson, J. G., and Evelyn, K. A. Clinical Studies of the Blood Volume. IV. Adaptation of the Method to Photoelectric Microcolorimeter, *J. Clin. Investigation* **17** 153, 1938.

4 Rourke, M. D., and Ernstene, A. C. A Method for Correcting the Erythrocyte Sedimentation Rate for Variations in the Cell Volume Percentage of Blood, *J. Clin. Investigation* **8** 545, 1930.

5 Daland, G. A., and Worthley, K. The Resistance of Red Blood Cells to Hemolysis in Hypotonic Solutions of Sodium Chloride, *J. Lab. & Clin. Med.* **20** 1122, 1935.

6 Moritz, F., and von Tabora, D. Ueber eine Methode, beim Menschen den Druck in oberflächlichen Venen exakt zu bestimmen, *Deutsches Arch. f. klin. Med.* **98** 475, 1910.

7 Malloy, H. T., and Evelyn, K. A. The Determination of Bilirubin with the Photoelectric Colorimeter, *J. Biol. Chem.* **119** 481, 1937.

8 Watson, C. J. Studies of Urobilinogen. I. Improved Method of Quantitation, *Am. J. Clin. Path.* **6** 458, 1936.

or minus 20 per cent when the daily excretion was less. The average of the duplicate analyses appears in the tables. Reticulocyte counts were done on smears made on brilliant cresyl blue stain and counterstained with Wright's stain. One thousand red blood cells were examined on each of two preparations. If the difference in the reticulocyte percentage exceeded 0.3 per cent, fresh preparations were obtained and examined.

MATERIAL

Five ward patients with uncomplicated chronic congestive heart failure were studied in detail. Fifteen investigations were initiated, but ten were discontinued because of diabetic acidosis, uremia, pulmonary infarcts with hemoptysis, bronchial asthma or death. Four of the 5 completely studied patients showed peripheral evidences of congestive heart failure, and 1 patient had predominantly left ventricular failure. Studies were begun within a few hours after the patients were admitted to the hospital and extended over periods ranging from seventeen to forty-one days. The usual medical measures were utilized in the treatment of these patients.

REPORT OF CASES

CASE 1—B L, a 58 year old man, was admitted to the hospital on Nov 22, 1938. The patient first noticed increasing dyspnea on exertion three years before his admission. A chronic cough, productive of mucopurulent sputum, had been present for over twenty years. In the year preceding admission there had been exacerbation of the cough with orthopnea, dyspnea on slight exertion and slight edema of the ankles.

On admission the patient was extremely cyanotic and moderately orthopneic and dyspneic, he had a frequent harassing cough, productive of tenacious mucopurulent material. The heart was markedly enlarged to the right and to the left, with regular sinus rhythm. Blood pressure was 140 systolic and 90 diastolic. The lungs were filled with coarse rhonchi, and there were moist rales at both bases. The liver was tender and extended two fingerbreadths below the costal margin. There was no ascites or sacral edema and but minimal edema of the ankles. The nonprotein nitrogen of the blood was 40 mg per hundred cubic centimeters.

Course—The patient rapidly lost weight after mercurial diuresis. The cough, orthopnea, dyspnea and edema decreased, as did the cyanosis. Complete digitalization was attained by the fourth day, when marked clinical improvement was already noted. However, the patient at no time became entirely free of orthopnea. He continued to gain weight during rest in bed and required frequent administration of mercurial diuretics. He was discharged on Jan 1, 1938, markedly improved but still with slight congestive failure.

CASE 2—J N, a 62 year old man, was admitted to the hospital on Oct 15, 1938. The patient complained of frequency of urination and nocturia of fifteen years' duration. Six months previous to the present admission, edema of the ankles and rales at the bases of the lungs were noted and successfully treated with rest in bed and the administration of digitalis. Three months before the present admission there was an episode of paroxysmal nocturnal dyspnea. Following this there were increasing dyspnea on exertion and orthopnea. The latter caused the patient to sleep in the sitting position for several weeks preceding admission. Edema of the ankles, first noted two months previously, became more marked and finally was not relieved by rest in bed.

Physical examination revealed a well nourished white man, sitting upright in bed, slightly dyspneic and markedly orthopneic. There was no cyanosis. The patient was not well orientated, and comprehension was poor. The heart was enlarged and overactive, the pulse was regular in rhythm. The blood pressure was 170 systolic and 98 diastolic. There were a small right hydrothorax and a few moist rales at the bases of both lungs. The liver was palpable three fingerbreadths below the costal margin. No other abdominal viscera were palpable, and no ascites

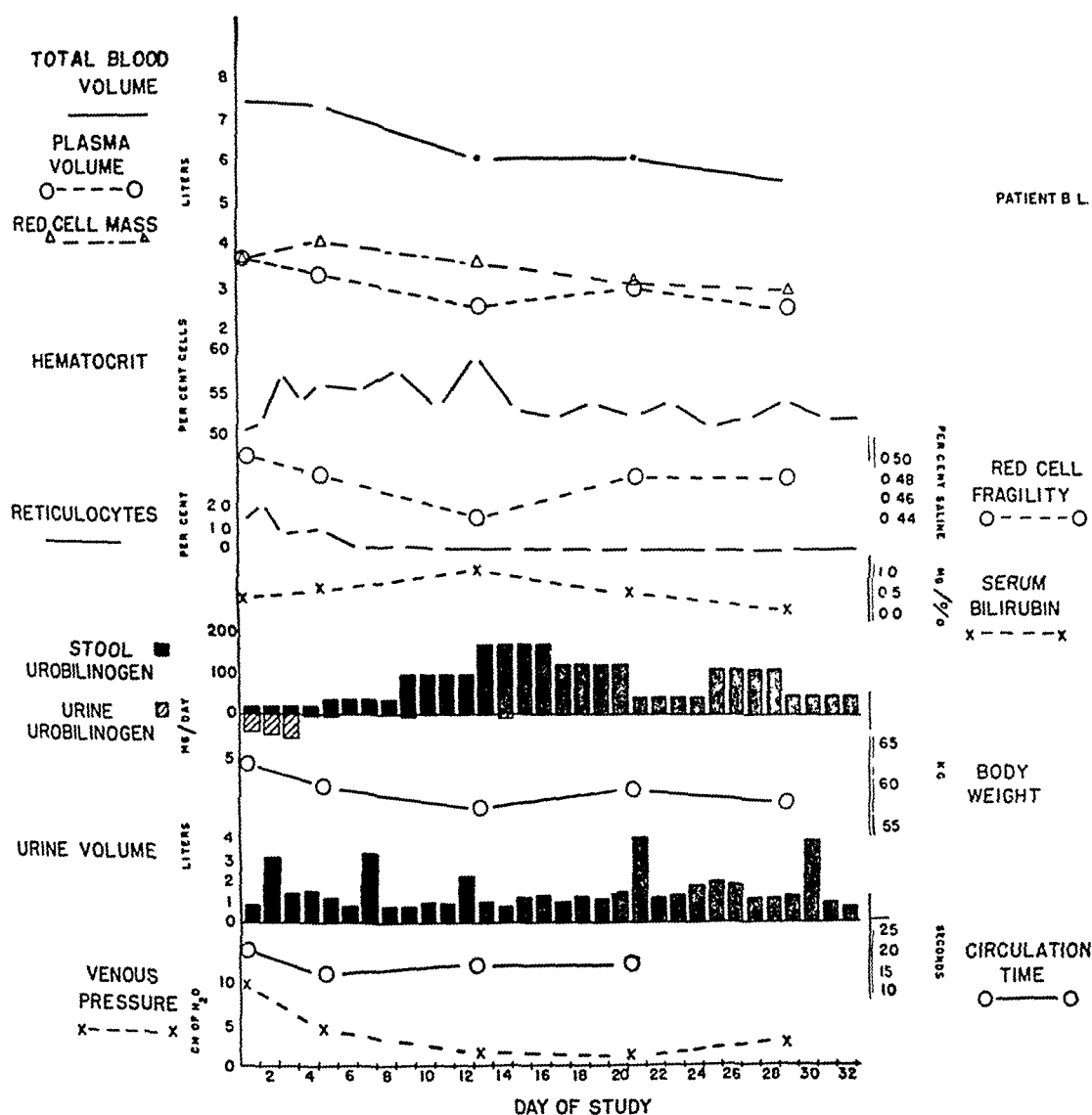


Chart 1—Graphic presentation of findings in case 1, that of B. L., a 58 year old man, 162 cm in height. The diagnoses were generalized arteriosclerosis, arteriosclerosis of the coronary arteries, congestive heart failure, chronic bronchitis and emphysema. (Normal calculated blood volume, 4,400 cc.)

was present. There was but minimal pretibial pitting edema. No prostatic enlargement was demonstrable. The urine contained no albumin and only occasional white blood cells. The nonprotein nitrogen of the blood was 36 mg per hundred cubic centimeters.

Course—The patient was digitalized and was given a salt-poor diet and a restricted fluid intake. By this regimen the frequency of urination and orthopnea were completely relieved. No pulmonary rales or edema of the ankles was

evident after the fourth hospital day. The patient was free of all signs and symptoms on the seventh hospital day, and on the nineteenth day he was allowed lavatory privileges. He was discharged on Nov 5, 1938, at which time he was still free of all signs and symptoms of congestive failure.

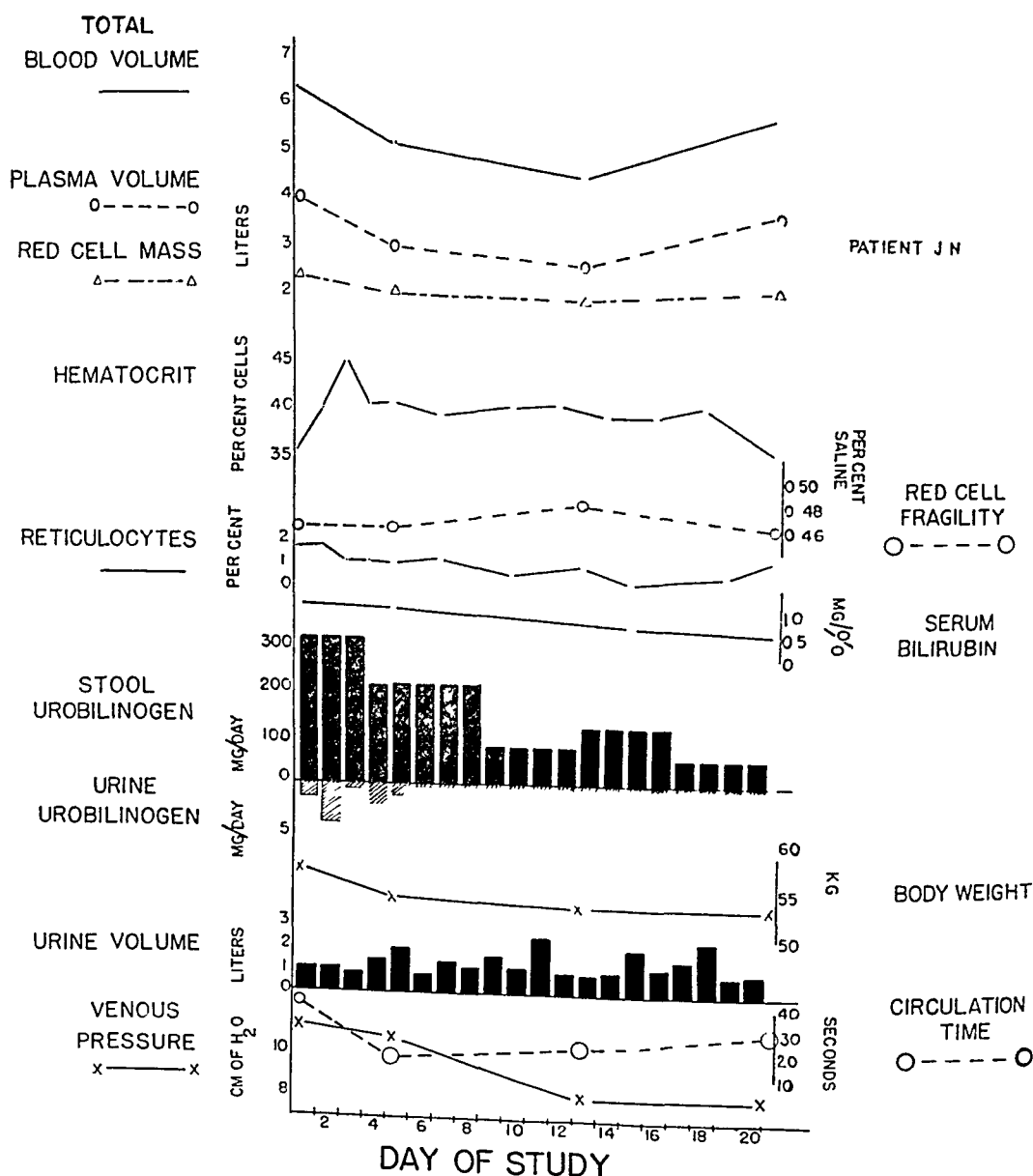


Chart 2—Graphic presentation of findings in case 2, that of J N, a 62 year old man, 160 cm in height. The diagnoses were arterial hypertension, arteriosclerosis, arteriosclerosis of the coronary arteries, congestive heart failure and cystitis (Normal calculated blood volume, 4,400 cc).

CASE 3—J G, a 53 year old woman, was admitted to the hospital on Feb 15, 1938. The patient first noticed slight dyspnea on exertion six years before the present admission and shortly thereafter began to have episodes of paroxysmal nocturnal dyspnea. These increased in frequency as the dyspnea on exertion became more severe. A year later edema of the ankles made its first appearance,

and several months later the abdomen began to swell. The first admission to this hospital, three years previously, resulted in complete disappearance of cyanosis, orthopnea, paroxysmal dyspnea and edema. A return to normal activity, however, brought on a recurrence of dyspnea, both paroxysmal and on exertion, as well as edema of the ankles and swelling of the abdomen. In the year preceding the present admission the patient remained constantly in bed, was orthopneic and never became free of edema.

On admission the patient was cyanotic, moderately dyspneic and orthopneic. The heart was enlarged to the left, the pulse was regular and rapid. Blood pressure was 280 systolic and 140 diastolic. Coarse rales were heard throughout both lungs, and there was flatness at the left base posteriorly. The liver was palpable four fingerbreadths below the costal margin, and the abdomen contained a moderate amount of fluid. The lower part of the legs and the ankles, as well as the lower part of the abdominal wall, were edematous. The nonprotein content of the blood was 30 mg per hundred cubic centimeters, and the total protein content of the blood was 6.8 per cent. Improvement was rapid as a result of mercurial diuresis and digitalization. The patient became free of edema and less orthopneic, but the cyanosis was still present when she was discharged from the hospital. In spite of a regimen of restricted fluid intake and oral diuretics, the repeated reappearance of edema of the ankles and rales in the lungs made frequent use of intravenous diuretics necessary. The patient was discharged to a hospital for patients with chronic diseases on March 28, 1938.

CASE 4—W. W., a 59 year old man, was admitted to the hospital on Jan. 17, 1938. Three years before the present admission the patient first noticed dyspnea on exertion. This became increasingly more severe and was soon followed by swelling of the ankles. During the first six months of illness large amounts of fluid were removed from the chest at another institution. During the next two and a half years the patient was completely incapacitated because of dyspnea at rest, orthopnea and marked swelling of the legs. During that time he was admitted to this hospital on three occasions, once in 1936 and twice in 1937. In the month preceding the present admission, despite continued digitalis and repeated intravenous mercurial diuretics, the patient became more edematous and more dyspneic. A continual cough with blood-tinged sputum appeared, as did periods of severe transitory substernal oppression.

On admission the patient seemed at the point of death. There was marked cyanosis and orthopnea, and breathing was in short gasps. Frequent cough was productive of large amounts of foamy, blood-tinged fluid. The pulse was rapid, with regular sinus rhythm. The blood pressure was 155 systolic and 110 diastolic. The right and left pleural cavities were flat to percussion up to the midscapular region. The abdomen was distended and filled with fluid, and the edge of the liver was not palpable, but tenderness in the right upper quadrant extended down to the umbilicus. There was marked pitting edema of the legs and of the entire abdominal wall. The nonprotein nitrogen content of the blood was 37 mg per hundred cubic centimeters.

Course—Immediately on admission bilateral thoracentesis was performed and a diuretic administered intravenously. The patient was placed in an oxygen tent. Within the first three hours there was definite subjective and objective improvement. Measurement of the blood volume was made six hours after admission. On the third hospital day the patient was removed from the oxygen tent. With repeated diureses he rapidly became free of detectable edema. By the eighteenth

day he was free of all signs of congestive heart failure, there was no edema, demonstrable hydrothorax or ascites and no orthopnea or dyspnea. The patient was maintained at rest in bed, with no further mercurial diuretics or gain in weight, until his discharge from the hospital on March 13, 1938.

CASE 5—D N, a 59 year old woman, was admitted to the hospital on Oct 5, 1938. The first admission to the hospital occurred five years previously for acute appendicitis. At that time there was no evidence of cardiac insufficiency, either by history or by physical examination. The patient remained perfectly well until three months prior to the present admission, at which time she noted pain in the right anterior portion of the chest, brought on by walking and disappearing with rest. Eight days before admission there was an episode of paroxysmal nocturnal dyspnea accompanied by wheezing, this had recurred nightly since that time. There were dyspnea on exertion, cough and generalized weakness of like duration. No swelling of the feet and no pain in the right upper quadrant of the abdomen was present.

On admission the patient was slightly cyanotic and orthopneic, but not dyspneic. There was no cardiac enlargement. Examination of the heart revealed regular sinus rhythm. The blood pressure was 170 systolic and 105 diastolic. Rales were present at the bases of both lungs posteriorly. The peripheral veins were not engorged, and the liver was not palpable. There was no pitting edema of legs or sacrum.

Course—The patient was given phenobarbital and theobromine with sodium acetate, and digitalization was carried out for four days. There was no recurrence of paroxysmal dyspnea or of angina pectoris. The rales in the lungs gradually disappeared. Mercurial diuretics, given intravenously on two occasions, caused no loss of weight or increased urinary output. The patient was discharged from the hospital on Oct 22, 1938, with no signs of heart failure.

RESULTS

Total Blood Volume—The 4 patients (tables 1, 2, 3 and 4, charts 1 and 2) with peripheral evidences of congestive heart failure had initial blood volumes varying from 125 per cent to 223 per cent of the expected normal calculated values according to height and sex.⁹ After clinical improvement, a decrease to normal calculated values in 2 patients and to 128 per cent and 196 per cent of normal in the other 2 patients was noted. One patient (table 5) with predominant left ventricular failure had a normal initial blood volume, with first a slight increase and then a slight decrease. One (table 2) had a distinct increase in total blood volume during the last few days of study, when he was allowed out of bed.

Changes in Red Blood Cell Volume and Plasma Volume—The blood volume increase observed at the beginning of the study consisted of

9 Gibson, J. G., and Evans, W. A. Clinical Studies of the Blood Volume. II. The Relation of Plasma and Total Blood Volume to Venous Pressure, Blood Velocity Rate, Physical Measurements, Age and Sex in Ninety Normal Humans, *J. Clin. Investigation* **16** 317, 1937.

TABLE 1—Findings in Case 1 (B L)† Diagnoses Generalized Arteriosclerosis, Arteriosclerosis of the Coronary Arteries, Congestive Heart Failure, Chronic Bronchitis and Emphysema

Days of Study	Weight, Kg	Total Blood Volume,† Cc	Plasma Volume,† Cc	Red Cell Mass,† Cc	Hemato crit,† Per Cent	Reticulo cytes, Per Cent	Serum Bilirubin, Mg per 100 Cc	Urine Volume, Average Cc per Day	Urinary Pigment, Average Mg per Day	Fecal Pigment, Average Mg per Day	Minimum Red Cell Fragility,† Per Cent Saline Solution	Venous Pressure,† Mm of Water	Circulation Time,† Seconds	Clinical Findings
1 4	63.5	7,100	3,700	3,700	50.4	1.2	0.3	1,490	2.0	19	0.50	100	21	Subsidence of cough and edema Loss of rales and cyanosis
5 8	60.0	7,300	3,250	4,050	56.0	0.5	0.5	1,290	Trace	31	0.18	15	15	
9 12	57.7				57.5	0.1		1,240	Trace	97				
13 16	57.2	6,050	2,540	3,510	59.0	0.0	1.0	1,050	Trace	138	0.41	20	17	Persistent orthopnea
17 20	59.5				52.0	0.0		1,212	0.0	119				
21 24	59.5	6,120	3,000	3,120	52.0	0.0	0.4	2,071	0.0	38	0.18	15	17	
25 28	60.0				51.0	0.0		1,190	0.0	108				Gaining weight at bed rest
29 32	58.2	5,650	2,655	2,995	54.0	0.0	0.2	1,753	0.0	38	0.48	30		

* The patient was a 58 year old man, 162 cm in height. The normal calculated blood volume is 4,400 cc

† These observations were made on the first day of each four day period

TABLE 2—Findings in Case 2 (J N)† Diagnoses Arterial Hypertension, Generalized Arteriosclerosis, Arteriosclerosis of the Coronary Arteries, Congestive Failure and Cystitis

Days of Study	Weight, Kg	Total Blood Volume,† Cc	Plasma Volume,† Cc	Red Cell Mass,† Cc	Hemato crit,† Per Cent	Reticulo cytes, Per Cent	Serum Bilirubin, Mg per 100 Cc	Urine Volume, Average Cc per Day	Urinary Pigment, Average Mg per Day	Fecal Pigment, Average Mg per Day	Minimum Red Cell Fragility,† Per Cent Saline Solution	Venous Pressure,† Mm of Water	Circulation Time,† Seconds	Clinical Findings
1 4	57.2	6,250	3,960	2,290	36.5	1.4	1.2	1,090	2.1	305	0.46	110	10	Loss of edema and rales Loss of orthopnea Free of all signs and symptoms of failure
5 8	51.5	5,620	2,990	2,630	41.7	1.2	1.1	1,275	0.8	210	0.16	105	17	
9 12	53.0				40.1	0.5		1,500	0.2	81				
13 16	52.7	4,450	2,610	1,840	41.9	0.6	0.7	1,250	0.2	125	0.48	80	22	Lavatory privileges Discharged symptom free
17 20	52.1				38.0	0.4		1,400	Trace	58				
21	53.0	5,610	3,660	1,950	35.7	1.1	0.6				0.16	80	27	

* The patient was a 62 year old man, 160 cm in height. The normal calculated blood volume is 4,100 cc

† These observations were made on the first day of each four day period

increase in both the plasma volume and the red blood cell volume, the percentage changes in red cell volume and plasma volume were approximately equivalent. The initial hematocrit values ranged from 37 to 53 per cent cells for the entire group of cases. During the early fall in the total blood volume in the course of recovery, the plasma volume usually decreased to a greater extent than the red cell volume, as evidenced by increase in the hematocrit value. As the blood volume dropped further, the hematocrit value returned to its previous status. In the instance already mentioned (table 2) in which the blood volume showed a secondary rise, the increase was due chiefly to an increase in plasma volume.

Reticulocyte Findings—For the 4 patients with peripheral evidences of congestive heart failure and increased blood volume the reticulocyte counts on admission to the hospital ranged from 12 to 27 per cent. During recovery the reticulocyte counts decreased for all of these patients to levels of 0.5 per cent or less. For 1 patient (table 2) in whom the blood volume increased when he was allowed up and about, the reticulocyte percentage increased slightly.

Fragility of the Erythrocytes—The initial values for the fragility of the red blood cells ranged from 0.46 to 0.52 for the 5 patients studied. Four of these values were 0.50 or 0.52, and for these patients (tables 1, 3, 4 and 5) the values decreased during recovery to 0.44 to 0.48. Values above 0.48 were not observed in this laboratory when the same technic was utilized on a group of normal subjects.

Excretion of Pigment—The excretion of blood pigment in the stools and urine was measured for the purpose of ascertaining whether there was a relation to changes in the total red blood cell mass. There was marked variation in the quantity of urobilinogen excreted in the various four day periods, this was noted in respect to the individual patient as well as in regard to the entire group studied. The quantity of pigment excreted in the feces for all the periods of study varied from 19 to 305 mg per day. For the patients of cases 2 and 4 the values for pigment excretion were seemingly related to the decrease in the total blood cell mass. The initial pigment excretion of 2 of the 5 patients was at or slightly above the maximum normal value (280 mg per day) reported by Watson.¹⁰

The urinary excretion of pigment of 2 patients (tables 3 and 4) was abnormally increased during the first period following admission to the hospital and decreased coincident with clinical improvement.

10 Watson, C. J. Studies of Urobilinogen. II Urobilinogen in the Urine and Feces of Subjects Without Evidence of Disease of the Liver or Biliary Tract, *Arch Int Med* 59:196 (Feb) 1937.

TABLE 3—Findings in Case 3 (J G)* Diagnoses Arterial Hypertension, Generalized Arteriosclerosis, Arteriosclerosis of the Coronary Arteries and Congestive Heart Failure

Days of Study	Weight, Kg	Total Blood Volume,†		Red Cell Mass,† Cc	Hemato crit,† Per Cent		Reticulo cytes, Per Cent		Serum Bilirubin, Mg per 100 Cc		Urine Volume, Average Cc per Day		Urinary Pigment, Average Mg per Day		Fecal Average Mg per Day		Red Cell Fragility,† Per Cent Saline Solution		Clinical Findings
1-4	96.5	8,500	4,150	4,350	53.2	2.7	2.7	1.8	1.8	1,242	14.0	282	0.52						Loss of ascites and sacral edema
5-8	87.2					2.0	2.0			742	2.5	71	0.54						Minimal ankle edema
9-12	86.4	7,900	3,720	4,180	54.1	0.9	0.9	1.3	1.3	380	2.1	119							Loss of cyanosis and rales
13-16	83.7					0.5	0.5			1,751	1.5	39							
17-20	82.4	7,700	3,760	3,940	51.7	0.7	0.7	1.4	1.4	298	0.9	137	0.52						Reappearance of rales and cyanosis
21-24	82.0					0.8	0.8			1,552	1.9	233							Persistent cyanosis, loss of rales
25-28	81.0	7,700	3,700	4,000	53.9	0.5	0.5	1.2	1.2	398	1.0	39	0.48						Reappearance of ankle edema
29-32	81.0					0.6	0.6			920	0.8	70							
33-36	79.6	7,600	3,680	3,920	52.6	0.7	0.7	1.4	1.4	1,170	6.0	124	0.48						Loss of edema
37-40	76.4					0.2	0.2			1,400	1.1	152							Discharged with cyanosis and orthopnea
41	75.0	7,230	3,520	3,710	51.5														

* The patient was a 53 year old woman, 162 cm in height. The normal calculated blood volume is 3,700 cc

† These observations were made on the first day of each four day period

Serum Bilirubin—The serum bilirubin was elevated in 3 (tables 2, 3 and 4) of the 4 patients with peripheral evidences of congestive failure and decreased during the period of hospitalization

COMMENT

An understanding of the metabolism of the blood is desirable in evaluating the changes, both clinical and physiologic, occurring in association with congestive heart failure. In the earliest stages of congestive failure, before the development of discernible edema and increased venous pressure, profound alterations in the circulatory dynamics are already present¹¹. These include definite venous engorgement together with increase in the cross-sectional diameter of the flowing blood stream and consequent slowed velocity of blood flow. When patients enter the hospital with pronounced signs of congestive failure the blood volume is greatly increased, as shown by the data of this study and of those of others¹. The level of the hematocrit under such circumstances is the result of the relative increase in plasma volume and red blood cell mass. The observed increase in the total red cell mass is to be related to active erythrocyte production, denoted by reticulocytosis.

During recovery from congestive failure, the blood volume decreases because of a reduction of the volume of both the plasma and the red cell mass, the reticulocyte percentage decreases. Before the first noticeable clinical improvement there is a preponderant reduction of the plasma volume¹⁰ as evidenced by the increase in the level of the hematocrit. This is followed by destruction of red cells and a further decrease in the total blood volume.

Pigment Excretion in the Stools—The amounts of urobilinogen excreted in the feces in the cases of this study were analyzed in relation to changes in blood volume as observed by serial measurements. The urobilinogen studies were made in an attempt to discover whether the destruction of red cells as indicated by measurements of blood volume taken during recovery from congestive heart failure would be reflected by increased excretion of the blood pigment.

In the case of 2 patients (tables 2 and 3) during the first period of observation the excretion of urobilinogen in the stools was at or above the upper limit for normal ambulatory patients reported by Watson¹⁰. There was in general no quantitative relation between reduction in the total red cell mass and the excretion of pigment in the stools¹².

11 Blumgart, H. L., and Weiss, S. Studies on the Velocity of Blood Flow. V. The Physiological and Pathological Significance of the Velocity of Blood Flow, *J. Clin. Investigation* 4: 199, 1927.

12 In studying normal ambulatory subjects Watson¹⁰ found that the daily excretion of urobilinogen calculated from four day periods varied from 40 to 280 mg and averaged 190 mg.

TABLE 4—Findings in Case 4 (W W) + Diagnoses Arterial Hypertension, Generalized Arteriosclerosis, Arteriosclerosis of the Coronary Arteries, Congestive Heart Failure, Angina Pectoris, Mitral Insufficiency and Aortic Stenosis

Days of Study	Weight, Kg	Total Blood Volume,† Cc	Plasma Volume,† Cc	Red Cell Mass,† Cc	Hemato crit,† Per Cent Cells	Reticulo cytes, Average Per Cent	Serum Bilirubin, Mg per 100 Cc	Urine Volume, Average Cc per Day	Urinary Pigment, Average Mg per Day	Fecal Pigment, Average Mg per Day	Minimum Red Cell Fragility,† Per Cent Saline Solution	Vital Capacity, Cc	Clinical Findings
1-4	66.1	5,880	3,330	2,550	44.4	1.8	4.0	850	18.0	148	0.52	1,200	Extremis, anasarca, cyanosis
5-8	63.6				42.0	1.2		2,449	10.5	199	0.46		
9-12	57.3	5,280	3,160	2,120	40.5	1.3	2.1	2,210	20.1	75	0.44		Loss of edema and anasarca
13-16						1.1		1,210	4.7	38		1,700	
17-20	48.6	4,560	2,540	2,023	44.0	0.0	1.5	1,047	3.0	40	0.44		No orthopnea, cyanosis or rales
21-24	47.1					0.0		927	2.8	27		2,500	No signs or symptoms of failure
25	46.8	4,620	2,672	1,948	41.2		1.6						

* The patient was a 59 year old man, 162 cm in height. The normal calculated blood volume is 4,600 cc.

† These observations were made on the first day of each four day period.

TABLE 5—Findings in Case 5 (D N) † Diagnoses Arterial Hypertension, Generalized Arteriosclerosis, Arteriosclerosis of the Coronary Arteries, Left Ventricular Failure and Angina Pectoris

Days of Study	Weight, Kg	Total Blood Volume,† Cc	Plasma Volume,† Cc	Red Cell Mass,† Cc	Hemato crit,† Per Cent Cells	Serum Bilirubin, Mg per 100 Cc	Urine Volume, Average Cc per Day	Urinary Pigment, Average Mm per Day	Fecal Pigment, Average Mg per Day	Minimum Red Cell Fragility,† Per Cent Saline Solution	Venous Pressure,† Mm of Water	Clinical Findings
1-4	62.2	3,625	2,155	1,370	39.6	0.3	815	0.2	54	0.50	90	Loss of cough and cyanosis
5-8	62.2						777	Trace	43			
9-12	61.3	4,070	2,624	1,446	36.8	0.3	440	Trace	88	0.48	85	Loss of rales and orthopnea
13-16	61.5						345	Trace	24			Symptom free
17	61.0	3,710	2,400	1,310	34.6	0.2				0.48	85	

* The patient was a 59 year old woman, 151 cm in height. The normal calculated blood volume is 3,500 cc.

† These observations were made on the first day of each four day period.

In five single periods of four days each in his observations of 5 patients with congestive failure, Watson¹³ failed to find an increased urobilinogen excretion in the stools. Ehrstrom,¹⁴ on the other hand, after using the method of Heilmeyer and Oetzel,¹⁵ concluded that fecal urobilinogen is increased coincident with or shortly after the decrease in reticulocyte percentage during congestive failure. It should be noted, however, that Heilmeyer and Oetzel, in a study of 14 normal subjects, found that the daily fecal excretion of urobilinogen, calculated from eight to ten day periods, ranged from 70 mg to 253 mg. Ehrstrom in observations on 1 normal subject found an average daily fecal output of 83 mg of urobilinogen. The fecal urobilinogen output of the 8 patients with congestive failure studied by Ehrstrom was in all instances well within the normal limits defined by Heilmeyer and Oetzel. Weiss¹⁶ also reported that the fecal output of urobilinogen associated with congestive failure in general shows a tendency to be increased, although the data show no distinct differences from the normal.

In general the results of our study, like the results of those already referred to, show during congestive failure no significant deviation from the normal values. The difficulties in interpreting the data are due to several causes. Variations in fecal urobilinogen output are great, making it more difficult to interpret values as abnormal unless they are clearly beyond the upper limits found in normal subjects. The normal values reported by Watson¹⁰ were observed in studies of ambulatory patients, and it is entirely possible that lower values would be observed for normal subjects kept in bed, who would therefore be in a state more comparable to that of patients with congestive failure. Watson¹⁰ found values ranging from 9 to 94 mg for 5 patients with mild infection, inanition or inactivity and no jaundice or anemia. Whether similar findings would be observed for normal subjects at rest in bed, who would serve as more suitable normal controls for the patients in our series, cannot be stated on the basis of the evidence now available. That lower values might be obtained for such persons is suggested by the fact that the fecal excretion of pigment in our series tended to be low at the conclusion of the various periods of observation, when the peripheral evidences of con-

13 Watson, C. J. Studies of Urobilinogen. III. The Per Diem Excretion of Urobilinogen in the Common Forms of Jaundice and Disease of the Liver, *Arch Int Med* **59** 206 (Feb.) 1937.

14 Ehrstrom, M. C. Blutstoffwechsel und Urobilinurie bei Herzinsuffizienz, *Acta med Scandinav* **88** 517, 1936.

15 Heilmeyer, L., and Oetzel, W. Blutfarbstoffwechselstudien. II. Ergebnisse bei Gersunden, Diätversuche. Der Blutfarbstoffwechsel im Hunger, *Deutsches Arch f klin Med* **171** 365, 1931.

16 Weiss, M. Ueber Urobilin und seine diagnostische Verwertung, *Wien Arch f inn Med* **20** 38, 1930.

gestive failure had either disappeared or were less marked (tables 1, 2 and 4). Repeated determinations on the same subjects suggest that the variations for a given person are less than those observed in different periods. With the exceptions of the patient (case 3) in whom orthopnea and cyanosis were still present at the end of observation, the values for the last period of study were less than 60 mg per day and averaged 41 mg for those patients who had shown signs of congestive failure (cases 1, 2 and 4). Although these results suggest an increased output of urobilinogen during the height of congestive failure, conclusions cannot confidently be drawn, particularly since there was no definite correlation in some instances between decreases in total cell mass and periods of increased fecal excretion of urobilinogen. The problem is made the more difficult by the fact that it is not certain that in all conditions the breakdown of hemoglobin will be reflected in increased amounts of urobilinogen in the stools. In this connection it should be noted that in certain instances of paroxysmal nocturnal hemoglobinuria, obvious marked blood destruction has been attended by no or only slight increased urobilinogen (or porphyrin) excretion.¹⁷

Urinary Excretion of Urobilinogen—The urinary excretion of urobilinogen of 2 of the patients studied (tables 3 and 4) was elevated in the presence of pronounced manifestations of congestive failure and diminished as clinical improvement occurred. The increased excretion of urobilinogen in the urine is evidently related to the decreased excretory function of the liver. In these 2 patients the liver was markedly enlarged. Similar observations have been reported by other investigators.¹⁸ In the cases of congestive failure studied by these authors, urobilinuria likewise was not of constant occurrence. In the 11 cases studied by Watson¹³ tenderness of the liver was regularly noted in those patients showing urobilinuria. Variations in urobilinuria were independent of the volume of urine excreted (tables 1 through 5).

Serum Bilirubin—Increases of serum bilirubin similar to those observed by us in studying some patients with congestive failure have been described by others.¹⁹ This elevated serum bilirubin is to be attributed to decreased function of the liver resulting from arterial anoxemia and congestion.¹⁹ In the absence of pulmonary infarction²⁰

17 Ham, T. H. Studies on Destruction of Red Blood Cells. I. Chronic Hemolytic Anemia with Paroxysmal Nocturnal Hemoglobinuria, an Investigation of the Mechanism of Hemolysis, with Observations on Five Cases, *Arch. Int. Med.* **64**: 1271 (Dec.) 1939.

18 (a) Jolliffe, N. Liver Function in Congestive Heart Failure, *J. Clin. Investigation* **8**: 419, 1930. (b) Watson¹³ (c) Weiss¹⁶

19 Fishberg, A. M. Heart Failure, Philadelphia, Lea & Febiger, 1937.

20 Keefer, C. S., and Resnick, W. H. Jaundice Following Pulmonary Infarction in Patients with Myocardial Insufficiency. I. A Clinical Study, *J. Clin. Investigation* **2**: 375, 1926.

the serum bilirubin rarely becomes sufficiently increased in persons with congestive failure to cause clinical jaundice¹⁹

Fragility of the Red Blood Cells—The fragility of the red blood cells was increased in the presence of congestive failure and was seemingly related to the degree of cyanosis clinically. With recovery, the minimum osmotic resistance of the red cells to hypotonic solutions of sodium chloride returned toward normal. Francescon²¹ and Greenthal and O'Donnell²² also noted this increased fragility of erythrocytes in association with congestive failure. The anoxemia and stasis of congestive failure are presumably responsible for the increased erythrocyte fragility, since complete arrest of the circulation of the arm in normal subjects by the blood pressure cuff likewise results in an increased fragility of the red blood cells. These studies are the subject of a separate communication by one of us²³

The finding of increased fragility in cases of congestive heart failure suggests that the anoxemia of this condition leads to an elevation of the serum bilirubin not only predominantly by its effect on liver function but also in part by causing an increased destruction of red blood cells.

Reticulocytosis—The finding of reticulocytosis, with the percentage of reticulocytes ranging from 12 to 27, in the 4 patients with peripheral evidences of congestive failure denotes active blood production stimulated by anoxemia. The degree of reticulocytosis observed by us is similar to that observed by Ehlistrom¹⁴. In other patients we have observed a percentage of reticulocytes as high as 48. Impaired oxygenation in other conditions likewise causes reticulocytosis. Szour and Bergenbaum²⁴ reported such changes accompanying chronic pulmonary tuberculosis, and similar findings are present in association with adaptation to atmosphere of low oxygen tension²⁵

21 Francescon, M. Comportamento della resistenza osmotica dei globuli rossi e del ricambio emoglobinico nei cardiopazienti in fase acuta di scompenso e in fase compensatoria, *Minerva med.* **37** 255, 1936.

22 Greenthal, R. M., and O'Donnell, W. S. Studies on the Fragility of the Red Blood Cells, *Am J Physiol* **58** 271, 1921.

23 Waller, J. V. Cause of Increased Fragility of Erythrocytes in Congestive Heart Failure, *Proc Soc Exper Biol & Med* **42** 64, 1939.

24 Szour, M., and Bergenbaum, C. Retikulozytenuntersuchungen bei Lungentuberkulose, *Wien klin Wchnschr* **47** 1583, 1934.

25 Barcroft, J., Binger, C. A., Bock, A. V., Boggart, J. H., Forbes, H. S., Harrop, G., Meakins, J. C., and Redfield, A. C. Report to the Peru High-Altitude Committee. VIII. Observations upon the Effect of High Altitude on the Physiological Processes of the Human Body, Carried Out in the Peruvian Andes, Chiefly Cerro de Pasco, *Phil Tr Roy Soc London* **211** 350, 1923.

SUMMARY AND CONCLUSIONS

We believe that in relating the data observed in our studies to each other and to the clinical manifestations of congestive heart failure, certain general conclusions can be stated. In the presence of pronounced manifestations of congestive heart failure with increased venous engorgement and elevated pressure, the plasma volume and total red cell mass are increased, the red cell fragility is increased and the reticulocyte percentage is elevated. The excretion of urobilinogen in the urine and the serum bilirubin concentration are frequently elevated, probably as a result of the impaired liver function resulting from anoxemia. As clinical recovery progresses and the total blood volume decreases, the loss in plasma tends at first to be somewhat greater than the decrease in total red cell mass, resulting in a slight temporary elevation of the hematocrit. The excretion of urobilinogen in the stools, although at no time significantly increased above the normal values for ambulatory patients, generally shows higher values during the periods of blood destruction than when the evidences of congestive failure become less marked. During the phase of contracting blood volume the reticulocyte percentage decreases, while the values for red cell fragility, serum bilirubin and urinary urobilinogen become normal.

COMPARISON OF SULFATHIAZOLE AND SULFAPYRIDINE IN TREATMENT OF PNEUMOCOCCIC PNEUMONIA

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The comparative effectiveness and toxicity of sulfathiazole 2-sulfanilamidothiazole and sulfapyridine in the treatment of pneumococcic pneumonia has been reported by Flippin, Schwartz and Rose¹ The corrected mortality for the sulfathiazole-treated series was 7.4 per cent and for the sulfapyridine-treated series 11.4 per cent Sulfapyridine reduced the temperature more rapidly than sulfathiazole, but the average number of hospital days for patients in the two groups was the same, thirteen and two-tenths days The severity and frequency of nausea and vomiting were less in the group of patients treated with sulfathiazole Other toxic manifestations were approximately equally frequent

At Cleveland City Hospital from January to June 1940, 40 patients with typed pneumococcic pneumonia were treated with sulfathiazole² and 62 with sulfapyridine Eighteen extremely ill patients (5 in the sulfathiazole-treated group and 13 in the sulfapyridine-treated group) received specific antipneumococcus serum intravenously in addition to chemotherapy One or more blood cultures, roentgen films of the chest, repeated blood counts, urinalyses and determinations of the free drug in the blood were made for every patient

DOSAGE

Sulfathiazole —The initial dose of sulfathiazole was 4 Gm by mouth, repeated in four hours, followed by 2 Gm every four hours until clinical improvement occurred Then 1 Gm was given every four hours until the temperature was normal for two to three days and clinical improvement was definite The average total dose was 53.3 Gm in five and

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1 Flippin, H F, Schwartz, L, and Rose, S B The Comparative Effectiveness and Toxicity of Sulfathiazole and Sulfapyridine in Pneumococcic Pneumonia, *Ann Int Med* **13** 2038-2049 (May) 1940

2 Sulfathiazole was available for study through cooperation with the Squibb Institute for Medical Research and the Medical Research Division of the Winthrop Chemical Co, Inc

three-tenths days, or 10.1 Gm per day. This dose produced an average level of 5.8 mg of free sulfathiazole per hundred cubic centimeters of blood.

Sulfapyridine—The initial dose of sulfapyridine was 2 Gm, followed by 1 Gm every four hours for five doses and then 1 Gm every six hours until the temperature was normal for two to three days and clinical improvement was established. The average total dose was 34.4 Gm in six and eight-tenths days, or 5.1 Gm per day. This dose produced an

TABLE 1—*Distribution of Types, Bacteremia and Mortality*

Type	Sulfathiazole Treated Group				Sulfapyridine Treated Group			
	All Patients		Patients with Bacteremia		All Patients		Patients with Bacteremia	
	Number	Died	Number	Died	Number	Died	Number	Died
I	11	3	1	1	17	3	3	1
II	6				8	3	1	1
III	6	1	1	1	12	2		
IV	2				3	1		
V	2				2		1	
VI	1				1			
VII	4				4			
VIII	4		1		4		1	
IX	1	1						
X					1	1	1	1
XI					1	1		
XII					3			
XIV	2		1		1			
XVI					1			
XVIII					2			
XIX	1				1			
XXIII					1			
Total	40	5	4	2	62	11	7	3
Mortality per cent	12.5		50.0		17.7		42.8	
Corrected mortality per cent *	10.3		33.3		8.9		20.0	

* Seven patients (1 treated with sulfathiazole and 6 treated with sulfapyridine) who died within twenty-four hours after admission are excluded, 3 of these patients had bacteremia (1 treated with sulfathiazole and 2 treated with sulfapyridine).

average concentration of 5.4 mg of free sulfapyridine per hundred cubic centimeters of blood. With both drugs about 3,000 cc of fluid was given to each patient each day.

THERAPEUTIC RESULTS

The therapeutic results are tabulated in table 1. There were 5 deaths in the group treated with sulfathiazole (table 2) and 11 deaths in the group treated with sulfapyridine (table 3). Exclusive of the patients who were moribund on admission and died within twenty-four hours, the corrected mortality is 10.3 per cent for the sulfathiazole-treated group and 8.9 per cent for the sulfapyridine-treated group.

The average age of the patients treated with sulfathiazole was 38.1 years and that of the patients treated with sulfapyridine 44.8. Treatment was begun on the third and six-tenths day of the disease in the

TABLE 2—*Analysis of Causes of Death in the Sulfathiazole-Treated Group**

No	Age	Day of Disease Treatment Begun	Type	Blood Culture	Number of Lobes Involved	Total Dose of Drug, Gm	Amount of Total Serum, Units	Comment
1	41	22	IX	Negative	2	25	—	Rheumatic heart disease, mitral stenosis, cardiac failure, no response to treatment, no autopsy
2	68	2	I	Negative	4	72	—	No response to treatment, autopsy lobar pneumonia of right lung showing organization and resolution bronchopneumonia in left lung, abscesses in right lung, hepar lobatum
3	58	8	I	Positive	1	68	200,000	Response to treatment for 7 days relapse and death on 14th hospital day, no autopsy
4	54	3	I	Negative	3	86	—	Temporary response to treatment, relapsed, autopsy lobar pneumonia in right lung, abscess of upper lobe of right lung, chronic pyelonephritis, heart weight 500 Gm
5	46	2	III	Positive	3	6	—	Moribund on admission death in 10 hours, no autopsy

* The autopsies were performed by members of the staff of the department of pathology of Cleveland City Hospital, division chief, Dr H T Karsner

TABLE 3—*Analysis of Deaths in the Sulfapyridine-Treated Group**

No	Age	Day of Disease Treatment Begun	Type	Blood Culture	Number of Lobes Involved	Total Dose of Drug, Gm	Amount of Total Serum, Units	Comment
1	70	2	I	Negative	2	43	300,000	No response to treatment, no autopsy
2	76	3	I	Negative	2	22	—	No response to treatment, no autopsy
3	63	3	IV	Negative	2	27	200,000	Chronic alcoholism, pellagra, no response to treatment autopsy bilateral confluent bronchopneumonia
4	77	?	XI	Negative	2	28	—	Hypertensive heart disease with auricular fibrillation and cardiac failure, no response to treatment, no autopsy
5	50	14	I	Positive	2	50	—	No response to treatment, autopsy bilateral organizing bronchopneumonia with abscess formation, acute vegetative endocarditis of tricuspid valve
6	53	6	II	Positive	2	4 (vomiting at once)	—	Moribund on admission, death in 3½ hours, no autopsy
7	41	7	X	Positive	2	15	—	Moribund on admission rheumatic heart disease with severe cardiac failure, death in 15 hours, autopsy rheumatic heart disease, heart weight 710 Gm, bilateral bronchopneumonia
8	58	3	III	Negative	2	3	—	Moribund on admission death in 11 hours, no autopsy
9	37	9	II	Negative	4	12	—	Moribund on admission, death in 16 hours, autopsy lobar pneumonia in 4 lobes
10	84	21	III	Negative	3	4	—	Moribund on admission death in 20 hours, autopsy lobar pneumonia in 3 lobes, rheumatic heart disease, severe coronary arteriosclerosis
11	61	5	II	Negative	3	10	—	Moribund on admission, death in 18 hours, no autopsy

* The autopsies were performed by members of the staff of the department of pathology of Cleveland City Hospital division chief, Dr H T Karsner

sulfathiazole-treated group and on the fourth and four-tenths day in the sulfapyridine-treated group. An average of 1.6 lobes was involved in the patients receiving sulfathiazole and of 1.5 lobes in those receiving sulfapyridine. There was no statistically significant³ difference between the two groups as to sex and color.

EFFECT OF TREATMENT ON COURSE OF THE DISEASE

Exclusive of patients who died, there was a critical fall in temperature within twenty-four hours in 45.7 per cent of the sulfathiazole-treated group, as compared with 54.9 per cent of the sulfapyridine-treated group. At the end of forty-eight hours had a critical fall in temperature, as compared with an additional 13.7 per cent of the other group. In the former group 14.3 per cent had a normal temperature within twenty-four hours, an additional 14.3 per cent within forty-eight hours and an additional 20.0 per cent within seventy-two hours. In the latter group, 13.7 per cent had a normal temperature within twenty-four hours, an additional 33.3 per cent within forty-eight hours and an additional 5.9 per cent of seventy-two hours. After the temperature had once reached normal a secondary rise above 37.5 C (99.5 F) occurred in 71.4 per cent of the patients treated with sulfathiazole, as compared with 78.4 per cent of those who received sulfapyridine. In the majority of instances this was of no consequence. The average number of hospital days for patients in each group was identical, seventeen and four-tenths days.⁴

COMPLICATIONS

In the group treated with sulfathiazole, pleural effusion occurred in 2 patients (slight in 1), empyema in 1, slow resolution in 1 and pulmonary abscess in 2. In the group treated with sulfapyridine, empyema occurred in 4 patients, slow resolution in 1 and pulmonary abscess in 2.

TOXIC REACTIONS

Nausea and vomiting were the most frequent toxic reactions. One third of the patients receiving sulfathiazole experienced vomiting, but it was almost uniformly mild. Approximately one half of the patients treated with sulfapyridine vomited, and the vomiting was more severe.

³ In this article the term "significant" refers to a difference which could be produced by chance in less than 5 per cent of trials as demonstrated by application of the chi square test, "highly significant" refers to a difference so great that it could be produced by chance in less than 1 per cent of trials, again as demonstrated by application of the chi square test.

⁴ This does not include patients who died or who remained in the hospital for further study or treatment of accompanying conditions.

Crystals of the drug were found in the urine of 61.5 per cent of the patients receiving sulfathiazole and in 28.6 per cent of those receiving sulfapyridine. This difference is statistically highly significant. The incidence of microscopic hematuria was 18 per cent for sulfathiazole and 10.7 per cent for sulfapyridine. One patient receiving sulfathiazole had retention of nitrogenous products and oliguria for thirty-six hours, and another had renal colic (the renal disturbance was presumably due to crystals of the drug in both instances). The incidence of dermatitis was 7.7 per cent for sulfathiazole and 5.4 per cent for sulfapyridine. Granulocytopenia due to sulfathiazole was suspected in 1 instance, but the diagnosis was not established.

COMMENT

The experience of Cleveland City Hospital indicates that in the treatment of pneumococcic pneumonia approximately twice as much sulfathiazole as sulfapyridine is required to maintain an average concentration of 5 to 6 mg. of the free drug per hundred cubic centimeters of blood. In accordance with Flippin, Schwartz and Rose,¹ no significant difference in mortality between treatments with the two drugs was found. In the Cleveland series the patients treated with sulfapyridine were probably sicker, since they were 6.7 years older and had had their disease eight-tenths of a day longer. This is partially counteracted by the fact that the patients treated with sulfapyridine showed an average of one-tenth of a lobe less involvement and that more serum was used in this group.

In both the Philadelphia¹ and the Cleveland series, sulfapyridine was found to bring the temperature down more rapidly. When the figures from the two sources are combined it is found that of 123 patients treated with sulfathiazole, 60 (48.8 per cent) had a critical fall in temperature in twenty-four hours, whereas of 136 patients treated with sulfapyridine, 84 (61.8 per cent) had a critical fall in temperature in twenty-four hours. This difference is statistically significant. Likewise, of 123 patients treated with sulfathiazole, 50 (40.6 per cent) had a normal temperature in forty-eight hours, whereas of 136 patients treated with sulfapyridine, 84 (61.8 per cent) had a normal temperature in forty-eight hours. This difference is highly significant statistically. Of the 123 patients in the sulfathiazole-treated group, 31 (25.2 per cent) had a secondary rise in temperature, in contrast to 52 (38.2 per cent) of the 136 patients in the sulfapyridine-treated group. This difference is statistically significant. In both series the number of hospital days was the same for both groups.

Again, combination of the figures from both sources shows that vomiting is markedly less frequent during treatment with sulfathiazole, in

fact, the difference is statistically highly significant. Sulfathiazole caused crystals in the urine more often in the Cleveland series. Otherwise the incidence of toxic reactions was not significantly different.

SUMMARY

From January to June 1940, inclusive, 40 patients with typed pneumococcic pneumonia were treated with sulfathiazole and 62 patients with sulfapyridine. It was found that approximately twice as much sulfathiazole as sulfapyridine was required to maintain an average concentration of 5 to 6 mg of free drug per hundred cubic centimeters of blood. No significant difference in mortality between the two groups was demonstrated, the corrected mortality for the sulfathiazole group being 10.3 per cent and for sulfapyridine 8.9 per cent. Sulfapyridine brought the temperature down to normal more rapidly, but a secondary rise was more common. The length of stay in the hospital was the same in both groups. Sulfathiazole caused less vomiting but more crystals in the urine. Otherwise toxic manifestations were not significantly different.

ACACIA IN THE TREATMENT OF THE NEPHROTIC SYNDROME

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PHILADELPHIA

AND

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The use of acacia intravenously in the treatment of nephrotic edema was first employed in a systematic manner by Hartmann and his associates¹ in 1933. They reported careful observations on 6 patients, all children, 5 of whom showed a satisfactory diuretic response after acacia was used (table 1). The daily dose amounted to 1 to 2 Gm per kilogram of body weight in the majority of the cases. If necessary, administration was repeated at intervals of one day, two days or more. Of special interest is the observation of these authors that the renal lesion is likely to improve as diuresis is established, as was shown in their cases by a diminished amount of casts and a lessened degree of albuminuria. Improvement in renal function in 1 case was so great that a normal condition was completely reestablished, as was shown by absence of edema, normal urinary findings and a normal content of protein in the serum.

The reason for administration of acacia is obvious. The colloid osmotic pressure of the serum in cases of nephrotic edema is subnormal, and intravenous administration of a colloidal solution of acacia, of which a 6 per cent solution in physiologic solution of sodium chloride has a colloid osmotic pressure considerably higher than that of the serum of a patient with nephrotic edema, could be very helpful in restoring, at least in part, the deficient colloid osmotic pressure of the serum of the recipient. Thus, according to the generally accepted hypothesis of the pathologic physiology underlying the nephrotic type of edema, the water which is stored in the tissues in excess can be mobilized more readily and can be excreted with the urine.

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* At the time this work was done, Dr Goudsmit was a Fellow in Medicine of the Mayo Foundation

1 Hartmann, A F, Senn, M J E, Nelson, M, and Perley, A. The Use of Acacia in the Treatment of Edema, J A M A **100** 251-254 (Jan 28) 1933

Encouraged by the results obtained by Hartmann and his co-workers, Austin and McGuinness² decided to treat in similar fashion an adult patient who had acute nephritis in which nephrotic elements were outstanding. After administration of 120 Gm of acacia in 800 cc of hypertonic saline solution, a very serious syndrome developed which necessitated venesection for its relief, apparently this was due to a sudden and excessive increase in the volume of the circulating blood. However, almost simultaneously the edema started to become mobilized, and soon it had completely disappeared. Thus, in their report, while they substantiated the desirable diuretic effects which can be obtained through the use of acacia, the authors warned against the injection of large quantities of this substance within too brief a period.

TABLE 1—*Results of Treatment for Nephrotic Edema with Acacia Reported in the Literature*

Authors	Patients	Hospital Admissions	Results	
			Free or Nearly Free of Edema	Failures
Hartmann and others, ¹ 1933	6	6	5	1
Austin and McGuinness, ² 1933	1	1	1	
Dick, Warweg and Andersch, ³ 1935	4	4		4
Barach and Boyd, ⁴ 1935	2	2	2	
Boone, ⁵ 1937	1	1	1	
Lepore, ⁶ 1937	1	5	5	
Kerkhof, ⁸ 1937	1	1	1	..
Landis, ⁹ 1937	6	6	6	
Shelburne, ¹⁰ 1938	3	3	3	
Total	28	29	24	5

The experiences of Dick, Warweg and Andersch³ were much less favorable than those of Hartmann and his co-workers and of Austin and McGuinness. Hardly any improvement in the clinical condition of 4 children who had nephrotic edema could be attributed to the use of acacia. In their paper special attention was given the fact that the concentration of proteins, already considerably less than normal prior to treatment, usually underwent further decrease subsequent to administration of a solution of acacia. The therapy thus more or less defeated its own purpose. In addition, the authors noted a considerable degree of swelling of the liver after administration of the colloidal solution of acacia, and they stated that this should be an additional reason for

2 Austin, J. H., and McGuinness, A. C. Precaution Concerning the Treatment of Edema by Intravenous Administration of Acacia, *Tr. A. Am. Physicians* 48:276-282, 1933.

3 Dick, M. W., Warweg, E., and Andersch, M. Acacia in the Treatment of Nephrosis, *I. A. M. A.* 105:654-657 (Aug. 31) 1935.

caution in its use. It should be noted, however, that relatively large amounts of acacia were used by these authors. Thus, a girl 3 years of age received 285 Gm in four months, another girl, 2 years of age, 129 Gm in five weeks, a boy 6 years of age, 705 Gm in six and a half months, and a boy 10 years of age, 492 Gm in two and a half months.

Two cases of nephrotic edema in which acacia was used with considerable symptomatic improvement were reported by Barach and Boyd.⁴ Their second patient, a boy 4 years of age, experienced diuresis after one dose of 21 Gm of acacia, although all other treatment in the hospital during a period of seven months had been without effect. From that time on, the patient made a slow but satisfactory recovery.

Boone⁵ noted that a 17 year old boy who had nephrotic edema lost 22 pounds (10 Kg) after administration of acacia. A second course of acacia combined with a single injection of salyrgan (mersalyl) decreased the weight of the patient another 19.8 pounds (9 Kg). The loss took place at a rate of approximately 1½ pounds (0.7 Kg) a day, and the patient was dismissed with only a small amount of residual edema.

Four cases of nephrotic edema were studied by Lepore.⁶ In all of these a satisfactory response to acacia was obtained, the patients became nearly free of edema soon after acacia was administered. The author observed considerable increase in the volume of circulating plasma after injection of acacia, and in his opinion, which is fortified by a statement of Peters,⁷ this in turn was responsible for the diuretic response.

Kerkhof,⁸ in his study of colloid osmotic pressure of plasma as a factor in the formation of edema, reported 1 case of subacute glomerulonephritis with edema in which treatment with acacia gave gratifying results. Within three days 300 Gm was administered, raising the colloid osmotic pressure of the serum from 8 mm to 15 mm of mercury.

Landis⁹ also has observed copious diuresis in 6 cases of nephrotic edema after administration of acacia. In 1 of his cases the diuretic response did not occur until after administration of aminophylline (theophylline with ethylenediamine). However, prior to administration

4 Barach, J. H., and Boyd, D. M. Hypoproteinemic Nephrosis and Its Treatment with Acacia. Report of Two "Cured" Cases, *Am J M Sc* **189** 536-544 (April) 1935.

5 Boone, J. A. Gum Acacia in the Treatment of Nephritic Edema, *New England J Med* **216** 289-292 (Feb 18) 1937.

6 Lepore, M. J. Acacia Therapy in Nephrotic Edema, *Ann Int Med* **11** 285-296 (Aug) 1937.

7 Peters, J. P. *Body Water. The Exchange of Fluids in Man*, Springfield, Ill., Charles C. Thomas, Publisher, 1935.

8 Kerkhof, A. C. Plasma Colloid Osmotic Pressure as a Factor in Edema Formation and Edema Absorption, *Ann Int Med* **11** 867-880 (Dec) 1937.

9 Landis, E. M. Observations on Acacia Therapy in Nephrosis, *J A M A* **109** 2030-2034 (Dec 18) 1937.

of acacia the same drug had failed to produce diuresis, and in this connection the author suggested the possibility of a synergistic action between acacia and "ordinary" diuretics.

Three additional cases of nephrotic edema in which highly satisfactory results were obtained with the use of acacia have been reported by Shelburne¹⁰. The author stressed the point that acacia should be employed as a temporary agent to free the patient of edema while high protein diets are given to maintain the clinical improvement. Fishberg¹¹ stated that he obtained excellent diuresis in several cases by injection of acacia, "but in others, it failed."

Largely on the basis of the evidence submitted by Dick and his associates, McCann,¹² after reviewing (in 1936) the recent literature on Bright's disease, concluded that in view of such experiences "further use of acacia seems to be unwarranted." It would appear that this conclusion adequately depicts the contemporary opinion of many physicians who are treating patients with a nephrotic type of edema. Our experiences, gained especially during the last two years, in which rather extensive use of acacia was made, have been more favorable. Undesirable effects have been limited and have been relatively innocuous. At the same time, the incorporation of acacia in an effective and efficient reduction of edema in the vast majority of cases. A summary of our clinical experiences thus appears in order.

GENERAL CONSIDERATIONS

Early Experiences with Acacia—Prior to 1937 at the Mayo Clinic acacia had been used in only a few cases of nephrotic edema. One of us (M. W. B.),¹³ in 1936, stated that the results, although sometimes encouraging, had not been as good as those obtained by Hartmann and his associates but indicated that this might be due to lack of experience. Our particular interest in acacia as a therapeutic agent in the nephrotic type of edema was aroused in the spring of 1937, when a patient whose edema was resistant to many forms of diuretic therapy which are usually successful was treated with acacia. The case has been reported in detail

- 10 Shelburne, S. A. Rational Use of Acacia in Treatment of the Nephrotic Syndrome, J. A. M. A. **110** 1173-1176 (April 9) 1938
- 11 Fishberg, A. M. Hypertension and Nephritis, ed 4, Philadelphia J. C. & Febiger, 1939
- 12 McCann, W. S. Bright's Disease. A Review of Recent Literature. Arch. Int. Med. **57** 630-642 (March) 1936
- 13 Binger, M. W., in discussion on Hartmann, A. F. and Perley, A. M. Acacia in the Treatment of Nephrotic Edema. J. A. M. A. **106** 416 (Feb. 1) 1936

elsewhere, but a summary of the essential points is presented in the following paragraphs because of its unusual interest

A married woman aged 27 noticed an increase in weight eight weeks before registration at the clinic, followed somewhat later by swelling of the legs, decrease in the output of urine, increase in the size of the abdomen and swelling of such parts of the body as were dependent for more than a brief period. Physical examination gave essentially negative results except for a moderate amount of ascites and rather extensive edema of the lower part of the back, the labia and the legs. The volume of urine in the first twenty-four hours was 150 cc, the specific gravity was 1.043. The urine¹⁴ contained albumin grade 4 (on the basis of 1 to 4) and a few casts, but no erythrocytes. At the time of registration the concentration of urea in the blood was 42 mg, that of cholesterol 833 mg, and that of serum protein 4.4 Gm, per hundred cubic centimeters. The albumin-globulin ratio was 1.5. A diagnosis of chronic glomerulonephritis with marked nephrotic features was made.

Fluids were limited, and a salt-free, high protein diet was prescribed (chart 1). Potassium nitrate, ammonium nitrate, aminophylline, salyrgan and thyroid in addition to sodium bicarbonate, sucrose and dextrose given intravenously and an abdominal paracentesis, all were ineffective in reducing edema. On the eleventh day of hospitalization, 350 cc of a 6 per cent solution of acacia was injected intravenously. Satisfactory diuresis ensued, and the patient's weight decreased. A second injection, of 500 cc of a 6 per cent solution of acacia, the next day resulted in further diuresis and loss of weight. One day later, 2 cc of salyrgan produced an extremely satisfactory output of urine. A few days later, the patient was dismissed from the hospital entirely free of edema. During the six days following the first injection of acacia, the patient lost 23.5 pounds (10.7 Kg). The colloid osmotic pressure of the serum one day before dismissal was 79 mm of water.

Particularly striking in this case was the fact that diuretics, especially salyrgan, which had been completely ineffective on three occasions during the first part of the period of hospitalization, displayed all of their customary diuretic action after administration of acacia.

14 Urinalysis, blood urea determinations according to Van Slyke and Cullen and determinations of the blood urea clearance, concentration of cholesterol of the blood, concentration of the serum proteins and the albumin-globulin ratio were carried out according to the directions of J. C. Todd and A. H. Sanford (*Clinical Diagnosis by Laboratory Methods: A Working Manual of Clinical Pathology*, ed. 9, Philadelphia, W. B. Saunders Company, 1939). The colloid osmotic pressure of the serum was determined according to Butt and Keys, as described by Butt, Power and Keys. "The concentration of acacia in the serum, its rate of excretion and its effect on the colloid osmotic pressure following intravenous injection in cases of cirrhosis of the liver." The article (Butt, H. R., Power, M. H., and Keys, A. "The Concentration of Acacia in the Serum, Its Rate of Excretion, and Its Effect on the Colloid Osmotic Pressure Following Intravenous Injection in Cases of Cirrhosis of the Liver," *J. Lab. & Clin. Med.* **24**: 690-695 [April] 1939) also describes Power's method for determining the concentration of acacia in serum, which was employed in the present study.

Diagnostic Criteria—Since June 1937, 51 patients more than 14 years of age have received treatment for nephrotic edema at the Mayo Clinic. All had albuminuria grade 4, with or without casts or erythrocytes in the urinary sediment, an appreciably diminished content of protein in the serum, a lowered or inverted albumin-globulin ratio and diminished colloid osmotic pressure of the serum. In the large majority of the cases there were increased values for cholesterol in the blood.

The diagnosis in all these cases was subacute or chronic glomerulonephritis of the nephrotic type, with or without renal insufficiency. We

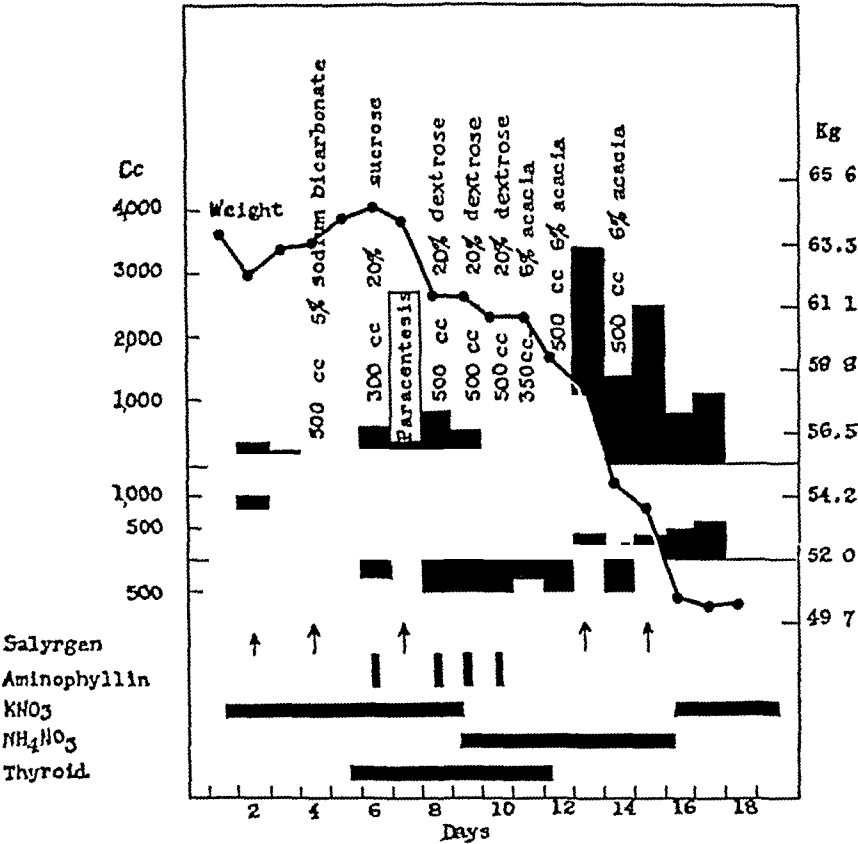


Chart 1 (case 1) —Essential factors of fluid balance in the case of a patient who had an unusually resistant type of nephrotic edema. Upper black blocks: volume of urine in each twenty-four hours. Lower black blocks: intake of fluid in each twenty-four hours (above zero line, oral intake, below zero line, intravenous intake), weight line as indicated. Medication: salyrgan (large arrow represents 2 cc given intravenously, small arrow, 1 cc), aminophylline, 4 grains (0.26 Gm) in 10 cc mixed with other solutions given intravenously, potassium nitrate and ammonium nitrate, 9 Gm orally, daily, and desiccated thyroid gland, 9 grains (0.6 Gm orally, daily). Reprinted from Goudsmit, A., and Binger, M. W. Nephrotic Type of Edema Unusually Resistant to Treatment. Report of Case, Proc. Staff Meet., Mayo Clin. **12**: 401-405 (June 30) 1937.

have refrained from using the diagnosis of "lipoid nephrosis" or "chronic nephrosis," since it appears that, although such a syndrome may exist entirely apart from chronic glomerulonephritis, one can never predict

whether sooner or later there will develop signs or symptoms such as erythrocytes in the urinary sediment, renal insufficiency or hypertension, which do not belong in the unadulterated picture of true lipoid nephrosis

General Regimen—All patients hospitalized for treatment of the nephrotic syndrome were given the standard salt-free¹⁵ diet with 75 to 100 Gm of protein per day. Various vitamins in the form of the pure crystalline compounds and concentrates were added to the diet in many instances. Fluids taken by mouth were limited to approximately 1,000 cc daily, or less if the patient was able to tolerate the restriction. Potassium or ammonium salts in the form of nitrates or chlorides regularly supplemented the regimen. Of these salts, in view of the experiences of Keith and Binger,¹⁶ potassium nitrate is preferred in the great majority of instances. It is given in the form of enteric coated pills of 0.5 Gm each. Six to 12 Gm per day is given with or after meals in doses of 2 to 4 Gm each. The most commonly employed dose was 9 Gm daily.

Necessity of Treatment for Edema—The appearance of a nephrotic type of edema in a case of chronic glomerulonephritis is a serious complication. The accumulation of fluid should be treated promptly and thoroughly for many reasons. 1. The presence of edema lessens resistance to infection. 2. If the edema is not treated, gastrointestinal disorders and anorexia develop, resulting in malnutrition. 3. It is common experience that, as a group, patients who have chronic glomerulonephritis without edema have a much better prognosis than those with equally efficient renal function (as determined by the level of urea in the blood or by urea clearance tests) but with the condition complicated by massive edema. The excessive amount of water present in the tissue spaces probably impairs proper functioning of all vital organs but may well be especially harmful to organs already the site of disease. 4. Patients who have progressive edema soon become unable to carry on their usual activities. 5. The presence and persistence of edema produce anxiety and are a great strain on the patient's mental stability.

Patients Treated Without Acacia—Of the 51 patients with nephrotic edema to whom treatment was given in the last two years, 14 became free of edema without the use of acacia (table 2). The success obtained in this group is tempered by the knowledge that if the patients had not

15 Of course the "freedom" from salt is only relative. Special bread and butter to which no extra salt is added during the processing must be employed. Milk, because of its rather high salt content, should be restricted. Thus, a so-called salt-free diet, served to contain approximately 2,000 calories per twenty-four hours, contains between 1 and 2 Gm of sodium chloride.

16 Keith, N. M., and Binger, M. W. Diuretic Action of Potassium Salts, *J. A. M. A.* **105** 1584-1591 (Nov. 16) 1935.

reacted so promptly to a more simple regimen treatment with acacia doubtless would have been instituted

Patients Treated with Acacia—Thirty-seven patients who had an uncomplicated nephrotic type of edema, 3 patients who had edema of mixed origin (partly nephrotic and partly nonnephrotic), 1 patient who

TABLE 2—Results of Treatment of Sixty-One Consecutive Hospitalized Patients* with the Nephrotic Syndrome at the Mayo Clinic Between July 1, 1937, and July 20, 1939

Clinical Condition	Treatment	Cases	Hospital Admissions	Results †		
				Free of Edema	Nearly Free of Edema	Failures
Nephrotic syndrome with edema	Diet alone	3	3	3		
	Diet and salyrgan	1	1	1		
	Diet and KNO ₃	10	10	10		
	Included acacia	37	47	25	13	9
Nephrotic syndrome with edema part of which was nonnephrotic in origin §	Included acacia	3	3	2	1	
Edema of acute exacerbation of chronic nephritis, associated exfoliative dermatitis	Included acacia	1	1		1	
Nephrotic syndrome without manifest edema	"Prophylactic" use of acacia	10	10			

* This number does not include 16 children up to 15 years of age who had the nephrotic syndrome and were seen during the same period
† In relation to number of hospital admissions
§ Histories of these 3 patients are presented in the text

TABLE 3—Distribution of Patients According to Age and Sex

Age, Years	Women		Men	
	Number	Per Cent	Number	Per Cent
15 to 24	5	33	7	28
25 to 34	7	47	4	16
35 to 44			5	20
45 to 54	2	13	4	16
55 to 64	1	7	3	12
65 to 74			2	8
Totals	15	100	25	100

had chronic nephritis and 10 patients who had the nephrotic syndrome without edema were treated with acacia (table 2) The distribution of these two groups according to age and sex is presented in table 3 The preponderance of men over women is evident and is worthy of note, since it is generally thought that women outnumber men in this regard However, 80 per cent of the women were less than 35 years of age, whereas only 44 per cent of the men were under 35 Thus, it appears that inclusion of a comparatively large number of older men materially

affects the general distribution. We are not prepared to say whether this truly represents a high incidence in the population at large or whether the high proportion of men in the present series was conditioned by special sociologic factors.

Renal Insufficiency—The incidence of renal insufficiency in the group receiving acacia was studied. Values for blood urea of 46 mg per hundred cubic centimeters or less were considered as indicative of fundamentally sufficient renal function, thus, only patients in whose cases the values for blood urea were consistently higher than this figure have been considered as having renal insufficiency (this criterion was proposed by one of us [Goudsmit] and Keith¹⁷). From the data available it appears that renal insufficiency of itself does not necessarily influence the outcome of diuretic treatment. Thus, of 33 patients with uncomplicated nephrotic edema successfully treated with acacia, renal insufficiency was noted in 13. Of 7 patients in whose cases satisfactory diuresis was not obtained with acacia, 3 had renal insufficiency.

TECHNIC, REACTIONS AND RESULTS

In the last few months we have employed a 6 per cent solution of acacia in 0.06 per cent sodium chloride. Before that time most of the acacia was prepared in our own laboratory for intravenous solutions.

Preparation of Solution of Acacia—Acacia in the form of lumps (pearls), no. 1, extra quality, is used. First, a solution of twofold strength (12 per cent) is prepared, this is then diluted to the required degree of concentration (6 per cent) with freshly triple-distilled water. Eight liters of this solution is prepared in the following manner: Weigh and place in a 4 liter beaker 480 Gm of crushed acacia. Add to this 500 cc of hot triple-distilled water, and stir with a glass rod. The acacia is extracted more readily if a small amount of hot water is added at a time. A large portion of the acacia dissolves rapidly. Carefully pour off from the residual material into a 12 liter round-bottomed pyrex flask the thick supernatant solution thus obtained. The residual material in the beaker is then reextracted of its acacia by adding another 500 cc of hot water and by stirring and pouring off the supernatant solution thus obtained. This process of extraction is repeated until all of the material is dissolved. To this solution is added 72 Gm of chemically pure sodium chloride,¹⁸ and the total volume contained in a 12 liter

17 Goudsmit, A., Jr., and Keith, N. M. *Relative Significance of Concentration of Inorganic Sulfate in the Serum and of Its Renal Clearance, with Special Reference to Diffuse Arteriolar Disease with Hypertension*, Arch. Int. Med. **66**: 816 (Oct.) 1940.

18 If a final concentration other than 0.9 per cent sodium chloride is desired a different amount must be added.

pyrex flask is then increased to 8 liters. This turbid solution is autoclaved at a pressure of 18 pounds (82 Kg) for periods of one hour on three consecutive days. This procedure results in the precipitation of some flocculent material. The solution, therefore, is thus filtered through a double layer of ordinary filter paper placed on top of a layer of cotton, which in turn rests on the funnel. The filtrate is reautoclaved a last time for one hour and then, under sterile conditions, is poured into sterile bottles.

Administration—The acacia was usually administered as a 6 per cent solution. At first a preparation in 0.9 per cent sodium chloride was used, later, in view of the desirability of limiting the intake of sodium chloride, acacia in distilled water was employed. Also, concentrations of sodium chloride of 0.06 per cent and 0.15 per cent were used. Therapeutically we have not been able to detect any differences in the results obtained by use of these various solutions. In most instances, 500 cc of a 6 per cent solution of acacia was given in one day, and forty-five

TABLE 4—Reactions Noted in the Course of One Hundred and Thirty Intravenous Injections of Solution of Acacia in Thirty-Three Patients with Successfully Treated Nephrotic Edema

Reaction	Number		Per Cent
	13	2	
Urticaria	2	5	10
Thoracic discomfort			2
Fever (with or without chill)			4

to seventy-five minutes was allowed for its administration. It was given every day or on alternate days, as it seemed best tolerated.

Dosage—The amount of acacia given in 41 instances in which it was successfully used in cases of nephrotic edema may be summarized as follows. In 17 cases, 90 Gm was given, and in 11 cases, 120 Gm. Only once was as much as 150 Gm and 156 Gm, respectively, given during one course of treatment, and in the remaining 11 cases the dose varied between 60 and 120 Gm. On completion of a course of acacia, the concentration of this substance in the serum was usually found to range between 1,000 and 2,500 mg per hundred cubic centimeters.

Undesirable Effects—A review of experience with 130 injections of acacia (table 4), comprising all cases of uncomplicated nephrotic edema treated successfully, reveals three different undesirable reactions which have occurred: (1) urticaria, (2) thoracic discomfort and (3) fever. Reactions of the urticarial type sometimes have been limited to the arm into which the injection was made but have occurred anywhere on the body shortly after the beginning of the injection or even a few hours after its completion. Subjective sensations of heat or flushing, in addition to

itching, sometimes accompanied the eruption. Usually the subcutaneous administration of 5 to 8 minims of epinephrine hydrochloride (1:1,000) will cope successfully with these symptoms, which in our experience have never lasted longer than twelve hours even without special medication.

Reactions in the form of thoracic discomfort are entirely subjective. They consist of substernal pain, dyspnea and sometimes sharp pain in the thorax, usually on the left side, sometimes there are diffuse thoracic pain and backache. This type of reaction is not accompanied by any changes in temperature, pulse or blood pressure, and nothing abnormal can be discovered on physical examination of the thorax. Subcutaneous injection of $\frac{1}{2}$ to 1 gram (0.032 to 0.065 Gm.) of codeine sulfate usually is sufficient to alleviate the symptoms, but they may persist to some degree for as long as eighteen hours.

Fever, when it occurs, does not differ essentially from the fever that sometimes develops after a blood transfusion. Sometimes fever is initiated by a chill. On one occasion the fever lasted for two days, although we suspect that an intercurrent infection of the respiratory tract played some part in the causation of this fever, it has been included in our tabulation of disagreeable reactions to acacia.

Frequently a patient who had had a reaction to acacia on one occasion would go without any untoward sign or symptom after a subsequent injection. Conversely, reactions have become apparent only with the second or third injection. Maytum and Magath,¹⁹ who reviewed experiences with 3,000 injections of a preparation of acacia similar to the one employed in the present series, mentioned only the development of hypersensitiveness as a hazard arising from its administration. We are confident that disagreeable reactions should be limited to the types noted by Maytum and Magath and by us, and we are convinced that the more serious reactions noted in the literature²⁰ must be due to inferior quality or improper preparation of the acacia.

Influence on Renal Function and on Blood Pressure—It is our experience that intravenous administration of solutions of acacia does not influence unfavorably an underlying glomerulonephritic type of lesion. Neither does its administration cause an increase in blood pressure for longer than a day. We have seen actual improvements in renal function subsequent to its use, as judged by the concentration of urea in the blood and by results from urea clearance tests. Also

19 Maytum, C. K., and Magath, T. B. Sensitivity to Acacia, Proc. Staff Meet., Mayo Clin. 7: 216-217 (April 13) 1932, Sensitivity to Acacia, J. A. M. A. 99: 2251-2252 (Dec. 31) 1932.

20 Studdiford, W. E. Severe and Fatal Reactions Following the Intravenous Use of Gum Acacia Glucose Infusions, Surg., Gynec. & Obst. 64: 772-784 (April) 1937.

secondary diffuse arteriolar disease with hypertension has become quiescent after treatment with acacia, as judged by return of the blood pressure to within normal limits and by disappearance of signs of active vasospastic retinitis

Additional Diuretic Measures—It is of interest to note (table 5) that more than half of the patients treated with restriction of diet, diuretic salts

TABLE 5—*Diuretic Measures Used in Addition to Dietary Regimen, Diuretic Salts and Acacia for Thirty-Three Patients (Thirty-Eight Hospital Admissions) with Uncomplicated Nephrotic Edema, Successfully Treated*

Therapy	Number of Hospital Admissions in Which Used	Percentage of Hospital Admissions
Salyrgan	11	29
Esidrone	2	5
Desiccated thyroid gland	4	11
Paracentesis	1	3
Transfusion	4	11
Theocalcin	1	3
Aminophylline	2	5
Any form of diuretic therapy in addition to dietary regimen, diuretic salts and acacia	18	47
No therapy other than dietary regimen, diuretic salts and acacia	20	53

TABLE 6—*Results of Combined Regimen of Treatment Including Injections of Solution of Acacia in Forty Consecutive Cases of Nephrotic Edema*

Status Obtained	First Hospital Admissions		Total Hospital Admissions	
	Number	Per Cent	Number	Per Cent
Entirely, or nearly free of edema at time of dismissal from hospital	36*	90	41	82
Status of edema essentially unchanged during period of hospitalization	4	10	9	18
Death (during period of hospitalization)	None			
Total	40	100	50	100

* One of these patients, one year after his dismissal from the hospital free of edema, was found to have normal urine, normal blood and normal renal function. This case of complete clinical remission is discussed in more detail in the text.

and acacia were not given additional diuretic agents. Mercurial diuretics were administered in about a third of the cases, and, judging from the diuretic response obtained, the usefulness in most cases appears questionable. Thus, in the course of 13 patients admitted to the hospital (table 5), for whom injections of salyrgan or of esidrone (the sodium salt of pyridinedimethylboxy- β -mercuri- ω -hydroxypropylamide-theophylline) or of both (on different occasions) were employed, the diuretic response was excellent in only 1, fair in another and in the remaining 11 either barely noticeable or absent.

Of the other diuretics employed, aminophylline was given intravenously, mixed with dextrose. In 2 cases treatment was complicated by comparatively advanced degrees of renal insufficiency. Theocalcin has been mentioned in table 5 because it has possible diuretic qualities. The direct indication for its administration, however, was diffuse arteriolar disease with hypertension superimposed on the original renal lesion.

In 1 case a transfusion of 500 cc of blood was followed by an increase of the output of urine, amounting to 2,800 cc in the ensuing

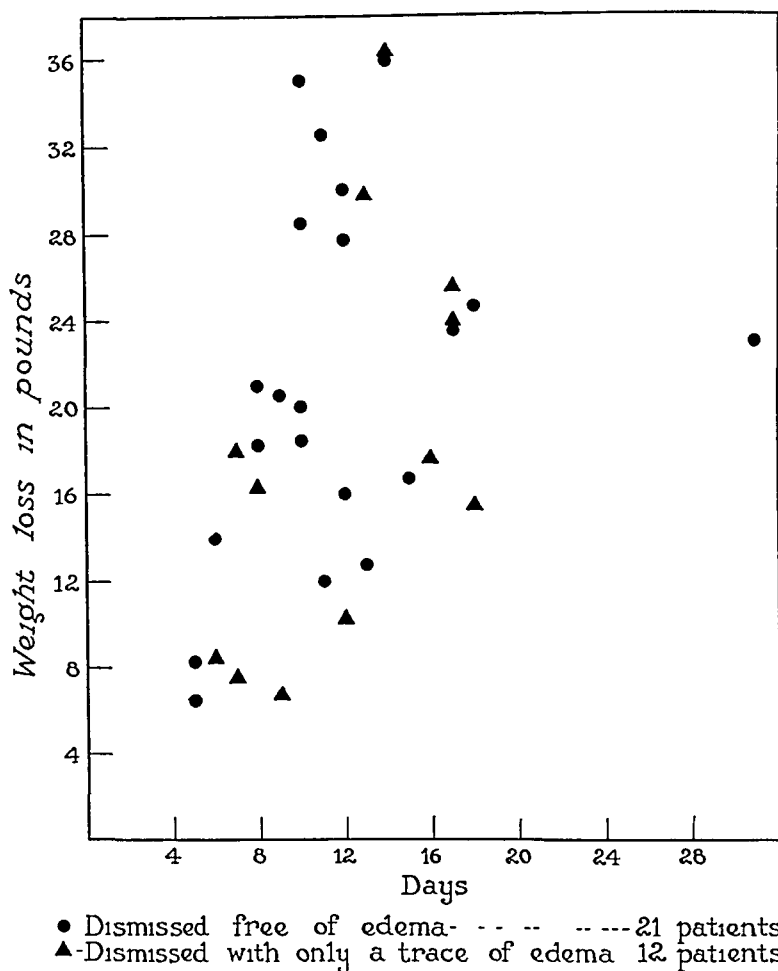


Chart 2—Relation of time to loss of weight and summary of observations on the first hospitalizations of 33 patients who had an uncomplicated nephrotic type of edema and who were treated successfully with acacia. The average weight lost by 15 patients was 2 pounds (0.9 Kg) or more per day, the average weight lost by 13 patients, 1 to 2 pounds (0.5 to 0.9 Kg) per day, the average weight lost by 5 patients, less than 1 pound (0.5 Kg) per day. Loss of weight due to mechanical elimination of fluid, e.g., by paracentesis or thoracentesis, has been subtracted. Thus the loss of weight represents the net weight lost through physiologic channels.

twenty-four hours. In other instances no beneficial effect on the edema was noticed. Thyroid has been used in an occasional case, but in this series we have not noted any beneficial effects from its administration.

Paracentesis has been advised for patients who have much mechanical embarrassment and who do not respond readily to diuretic treatment. As can be seen, its incidence in the present series was comparatively low. Thus, as a whole, additional diuretic measures appear to be of relatively little value as a supplement to the treatment with diet, diuretic salts and acacia.

Results—The results of the combined regimen of treatment, including injection of acacia, in 40 consecutive cases of nephrotic edema are summarized in table 6. It is evident that 90 per cent of the patients, at the time of their first admission to the hospital, could be relieved of edema. Some reasons for failure of treatment of the remaining 10 per cent will be considered later in this paper.

The rate at which the edema disappeared has been represented in chart 2. It is evident that, on an average, weight (edema fluid) was lost at a rate of between 1 and 2 pounds (0.5 and 0.9 Kg) per day. Even in those cases in which the response was relatively slow, a loss of nearly 1 pound (0.5 Kg) per day occurred.

REPORT OF CASES

CASE 1—This case has been mentioned earlier.

CASE 2—A boy 15 years of age was admitted to the clinic on July 5, 1938. In May 1938 he had had a cold of negligible severity, unaccompanied by a sore throat. A few days later, however, he had noticed edema around the ankles, soon followed by puffiness around the eyelids. Urinalysis elsewhere revealed marked albuminuria and a few erythrocytes in the urine. He was put to bed for five weeks, fluid was restricted and a low salt diet was prescribed. The edema, however, did not diminish. When the patient was admitted to the clinic few symptoms were noted other than those already enumerated. Fluid in the abdomen was not demonstrable. The blood pressure was 125 systolic and 75 diastolic. Examination of the ocular fundi gave negative results. The volume of urine for twelve hours was 200 cc, the specific gravity was 1.034. Urinalysis revealed albumin, grade 4, and granular casts, grade 3 plus, but no erythrocytes. On admission the concentration of urea was 60 mg, that of cholesterol, 490 mg, and that of serum proteins, 3.9 Gm per hundred cubic centimeters of blood. The albumin-globulin ratio was 1:1.14, and the colloid osmotic pressure of the serum was 66 mm of water. Because of the pus noted occasionally in the urine, a urologic investigation was made. This, including an excretory urographic study, gave entirely negative results. A diagnosis of subacute glomerulonephritis with nephrotic features was made.

The course in the hospital is illustrated in chart 3. The patient was given a salt-free diet with 70 to 75 Gm of protein daily, fluids were limited to 1,000 cc per day. Potassium nitrate, 9 Gm daily, was also prescribed, and potassium chloride was allowed as a substitute for salt. A course of injections of acacia was started on the second day. However, after having received 100 cc the patient complained of some substernal pain and dyspnea, and the injection was discontinued. One grain (0.06 Gm) of codeine sulfate was administered, with prompt subsidence of the unpleasant symptoms. Three days later the patient was able to tolerate 500 cc of a 6 per cent solution of acacia without any undesirable effects. On the fifth day he had started to lose weight and, continuing his progress, was

practically free of edema on the eleventh day, after having lost approximately 30 pounds (13.6 Kg)

One day after the last injection of acacia the concentration of serum proteins was 3.1 Gm per hundred cubic centimeters and the colloid osmotic pressure 91 mm of water. During treatment in the hospital, the value for blood urea decreased to 40 mg per hundred cubic centimeters, and three months later it was 24 mg. The patient was dismissed on the fifteenth day of hospitalization, free of edema and feeling very well. He was advised to continue the salt-free diet with 70 to 75 Gm of protein, to restrict the intake of fluid to 1,000 cc and to take 7.5 Gm of potassium nitrate per day.

The regimen followed in this case proved satisfactory and is the usual one employed in this type of case. Seldom are other diuretic measures necessary.

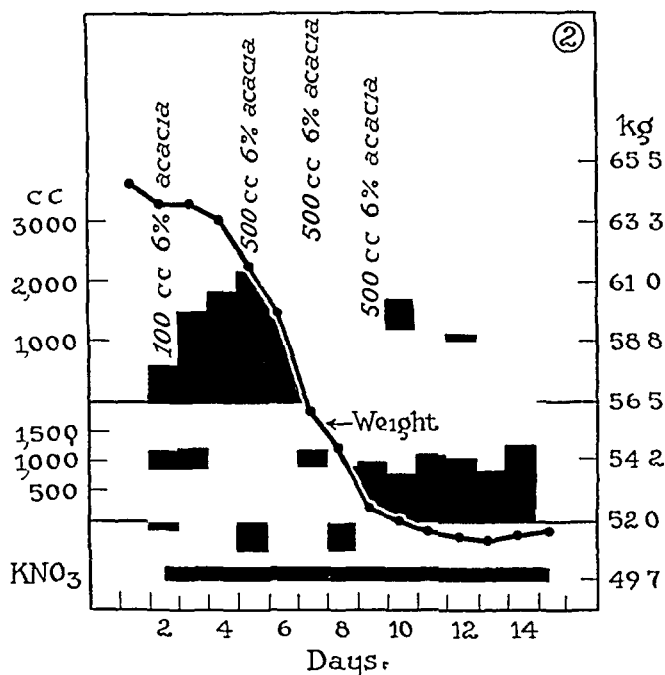


Chart 3 (case 2) —Essential factors of fluid balance in the case of a patient with nephrotic edema whose treatment consisted of special diet, restriction of fluids and administration of potassium nitrate (9 Gm daily) and acacia. This is a typical graph of an uncomplicated course in which prompt response to the regimen occurred. The details of the chart are explained in the legend of chart 1.

CASE 3—A white man aged 30, single, had noted painless edema of the legs and ankles for nine months, since January 1938. He also had noted a scanty volume of urine and had been told elsewhere that his urine contained a considerable amount of albumin. On his admission (August 6) extensive edema of the lower extremities as far as the hips was noted. The blood pressure was normal, and examination of the ocular fundi gave essentially negative results. The urine had a specific gravity of 1.023 and contained albumin, grade 4. Bence-Jones protein was not present, there were hyaline casts, grade 2 (on the basis of 1 to 4), granular casts, grade 2 (on the basis of 1 to 4) and erythrocytes, grade 1 (on the basis of 1 to 4). The concentration of urea was 44 mg, that of cholesterol, 877 mg and that of serum proteins, 3.9 Gm, per hundred cubic centimeters.

of blood. The albumin-globulin ratio was 1:1, and the colloid osmotic pressure of the serum was 110 mm of water. The diagnosis was chronic glomerulonephritis of the nephrotic type, with massive edema.

The patient was placed in the hospital (chart 4) on our standard regimen, and after the third day the edema began to disappear. Acacia was administered on four consecutive days, together with 9 Gm of potassium nitrate per day, this brought the daily volume of urine up to 2,400 cc. Salyrgan was given on the second day following admission, after the urinary output was 1,100 cc for twenty-four hours, on the next day without any diuretic measures except administration of potassium nitrate, the volume of urine amounted to 1,600 cc. On the eighth day of the patient's stay in the hospital another injection of salyrgan was given. Although the resulting output of urine amounted to 2,000 cc in twenty-

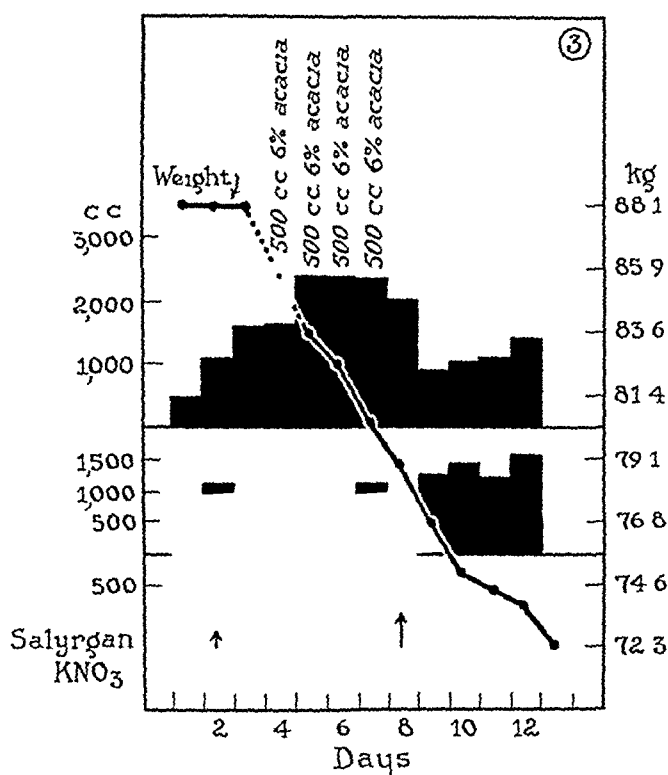


Chart 4 (case 3) —Essential factors of fluid balance in the case of a patient with nephrotic edema treated by the standard regimen supplemented with 9 Gm of potassium nitrate daily. Notice the slight diuretic response to salyrgan before acacia was given and the good volume of urine after the use of acacia. Successive days without salyrgan, however, show volumes of urine each twenty-four hours even larger than those with salyrgan. Thus, considering the course in the hospital as a whole, salyrgan did not add much to the regimen of diet, potassium nitrate and acacia. The details of the chart are explained in the legend of chart 1.

four hours, this was less than the diuresis which occurred on the days following administration of acacia. The patient was dismissed from the hospital on the thirteenth day, free of edema, and was advised to continue the regimen outlined.

This case illustrates two points previously mentioned. One is that in the majority of cases salyrgan does not add much to the effectiveness of treatment with diet, potassium nitrate and acacia. This is

brought out by the fact that the volume of urine secreted after the first administration of salyrgan, although larger than on the previous day, was not as large as on the following day, when salyrgan was not given, nor was the volume on the day of the second administration of salyrgan as large as on the three previous days, although it was considerably in excess of the volume for the subsequent day. Another important point is that this case illustrates the fact described by us, as well as by Landis, that diuretics appear to give better results after acacia has been given than before.

CASE 4—A white sailor aged 39 registered at the clinic Dec 17, 1937. He stated that in his work he had been exposed to frequent chilling and that in 1933, when he had a cold, he had noticed some puffiness under his eyes. At that time his physician had found albumin in the urine. The patient had stayed in bed for five days. In 1935, however, he had passed a life insurance examination. Later in the same year he had an experience similar to the one in 1933, the symptoms lasted only a few days. Two months before his registration at the clinic, after exposure to rather extreme conditions of moisture and cold, he had noticed puffiness of the ankles. On the fourth day he had felt sick, and on the fifth day he had noticed puffiness "all over." He was hospitalized elsewhere for five weeks and was put on a low salt diet with restriction of fluid to 1,000 cc a day. Nevertheless, he gained 25 pounds (11.3 Kg) during that period. After leaving the hospital, treatment with a high protein diet and administration of 2 Gm of thyroid extract three times daily had failed to improve his condition. One week before admission to the clinic the patient had been given an intramuscular injection, probably a mercurial diuretic, followed by an output of 4,200 cc of urine in the first twenty-four hours, a diuretic effect of lesser degree persisted for three more days.

Examination at the clinic revealed slight puffiness of the eyes and extensive edema of both legs. The blood pressure was 175 mm of mercury systolic and 100 mm diastolic. Examination of the ocular fundi gave essentially negative results. The urine had a specific gravity of 1.022. There were albumin, grade 4, hyaline casts, grade 1, granular casts, grade 2, erythrocytes, grade 1 and leukocytes, grade 2. The concentration of urea was 30 mg, that of cholesterol, 792 mg, and that of serum proteins, 4.0 Gm per hundred cubic centimeters of blood. The albumin-globulin ratio was 1:1.2, and the colloid osmotic pressure was 89 mm of water. The blood urea clearance amounted to 23.4 cc per minute, at a volume of 15 cc per hour. A diagnosis was made of chronic glomerulonephritis of the nephrotic type, with edema.

The course of this patient in the hospital is illustrated in chart 5. The scheme of treatment was essentially the same as that in cases 2 and 3. A few days after completion of the course of acacia, the colloid osmotic pressure of the serum was 93 mm of water, and the serum contained 1,500 mg of acacia per hundred cubic centimeters. The patient was dismissed from the hospital, free of edema, on the fourteenth day and was advised to continue on a low salt diet, to limit the intake of fluid to 1,000 cc daily and to take 100 Gm of protein a day and 2.5 Gm of potassium nitrate three times a day for five days in each week.

One month after his dismissal, the patient returned for reexamination. He had gained 4 pounds (1.8 Kg), and some edema of the legs was present. The specific gravity of the urine was 1.036, there were albumin, grade 4, hyaline casts, grade 1, and erythrocytes, grade 1. The concentration of urea was 38 mg

and that of serum proteins 32 Gm per hundred cubic centimeters of blood. The blood urea clearance amounted to 549 cc per minute at a volume of 340 cc per hour. The colloid osmotic pressure of the serum was 76 mm of water. The patient was given two more injections of acacia, which raised the colloid osmotic pressure to 106 mm of water and the concentration of acacia in the serum from 1,240 to 1,860 mg per hundred cubic centimeters. The patient was advised to continue the regimen as outlined.

One year later, in January 1939, he returned to the clinic for reexamination. He stated that he had been able gradually to cut down the amount of potassium nitrate taken, while remaining free of edema. He was feeling very well. General examination gave negative results, and his weight was the same as the weight

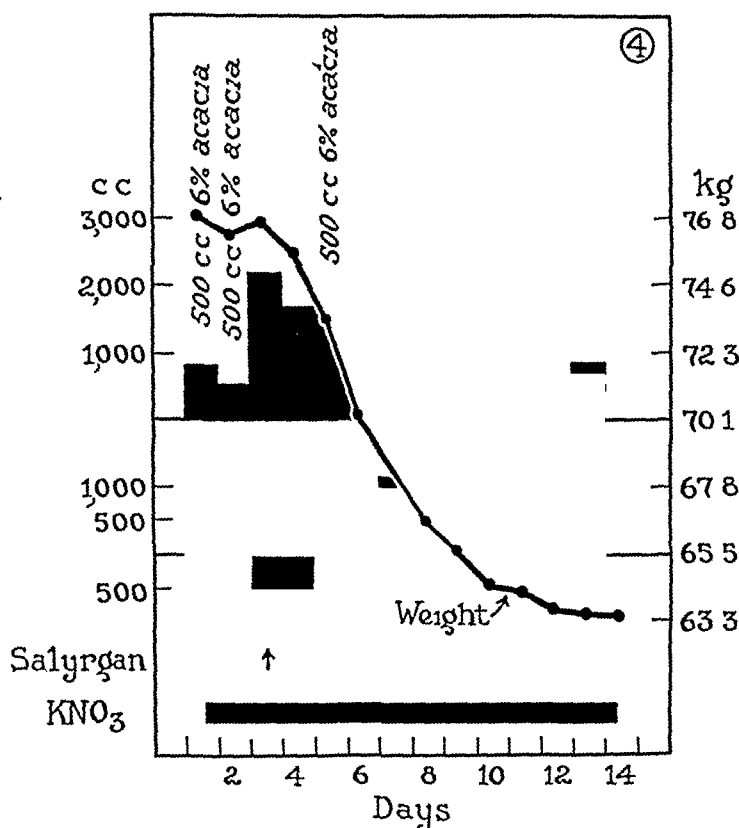


Chart 5 (case 4)—Essential factors of fluid balance in the case of a patient with nephrotic edema who made a complete recovery (clinical cure) subsequent to dismissal from the hospital. He was given potassium nitrate, 9 Gm daily, and salyrgan, 1 cc (intravenously), with fairly good response. Clinically, the course in the hospital was not different from that of the other patients described. The details of the chart are explained in the legend of chart 1.

recorded on his dismissal from the hospital. The specific gravity of the urine was 1.030, albumin was not present. The concentration of urea was 38 mg per hundred cubic centimeters of blood, the blood urea clearance amounted to 73 cc per minute at a volume of 440 cc per hour. The concentration of serum proteins was 7.5 Gm per hundred cubic centimeters, and the colloid osmotic pressure of the serum was 405 mm of water.

The complete clinical remission in this case was certainly gratifying. It allows one to look somewhat more optimistically on the many cases

in which a diagnosis of chronic glomerulonephritis with predominant nephrotic features appears the one best suited to the history and the pathologic picture. We realize that the diuretic measures employed cannot be held directly responsible for this remarkable remission, however, the clinical course definitely shows that treatment with acacia does not interfere with healing processes in the kidney.

CASE 5—A white man aged 38 was admitted to the hospital Jan 3, 1939, because of recurrence of swelling of the legs for the previous two weeks.

He had been hospitalized by physicians at the Mayo Clinic ten weeks previously, at which time a diagnosis of chronic glomerulonephritis with nephrotic features had been made. At that time he had completed successfully the standard treatment with a low salt diet, potassium nitrate and acacia and had lost 16 pounds (7.3 Kg) in twelve days. He had been dismissed free of edema and was instructed to continue with his special diet, potassium nitrate and restriction of fluids. However, after approximately six weeks he had experienced gastrointestinal symptoms, and the administration of potassium nitrate was discontinued. It was at this time that the patient had noticed recurrence of edema.

At the time of his readmission to the hospital the content of acacia in the serum amounted to 225 mg per hundred cubic centimeters, which was approximately 15 per cent of the estimated concentration at the end of the first period of hospitalization. The concentration of serum proteins was 3.1 Gm per hundred cubic centimeters, and the albumin-globulin ratio was 1:1. On his first admission the concentration of plasma proteins was 3.4 Gm per hundred cubic centimeters and the albumin-globulin ratio was 1:1.

Diuretic salts were not administered until the eighth day of hospitalization (chart 6). The patient received the standard diet, and on the third day treatment with acacia was started. Abundant diuresis promptly ensued, and in five days the patient lost 14 pounds (6.4 Kg). One day, after the third injection of acacia, the colloid osmotic pressure of the serum was 95 mm of water, and the serum contained 1,770 mg of acacia per hundred cubic centimeters. Addition of potassium chloride to the regimen at this time had essentially no further effect. A final dose of acacia on the tenth day was followed again by diuresis. The patient was dismissed, free of edema, on the fourteenth day after his entrance into the hospital.

As was stated earlier in this paper, the most efficient treatment of the patient who has a nephrotic type of edema incorporates dietary measures and administration of potassium nitrate and acacia. Even though particularly striking results can be obtained with otherwise resistant nephrotic edema, one is justified in questioning for a moment the essential value of acacia in a complicated regimen like this. However, in case 5, potassium nitrate was not well tolerated, and its omission from the regimen supplied us with an interesting experiment in obtaining evidence of diuretic action of acacia without benefit of diuretic salts. In case 6 a prolonged regimen with potassium nitrate was supplemented with occasional injections of acacia and thus gave us additional opportunity to study the effects of the acacia itself. The results in case 5

support the view that acacia has properties by which it definitely facilitates the mobilization of fluid and its elimination in the urine in the nephrotic type of edema. The colloid osmotic pressure, however, at the time when diuresis was taking place efficiently was considerably subnormal.

CASE 6—A white painter aged 47 registered at the clinic April 13, 1939. He stated that in September 1938 he began to experience rather frequent severe headaches. His blood pressure at that time was 182 mm of mercury systolic and 120 mm diastolic. In January 1939 severe pitting edema of the ankles had developed. Examination elsewhere showed a severe degree of albuminuria. Toward the end of February he had contracted influenza, and he noted a considerable increase in the amount of edema. Later the abdomen appeared to be swollen. On examination,

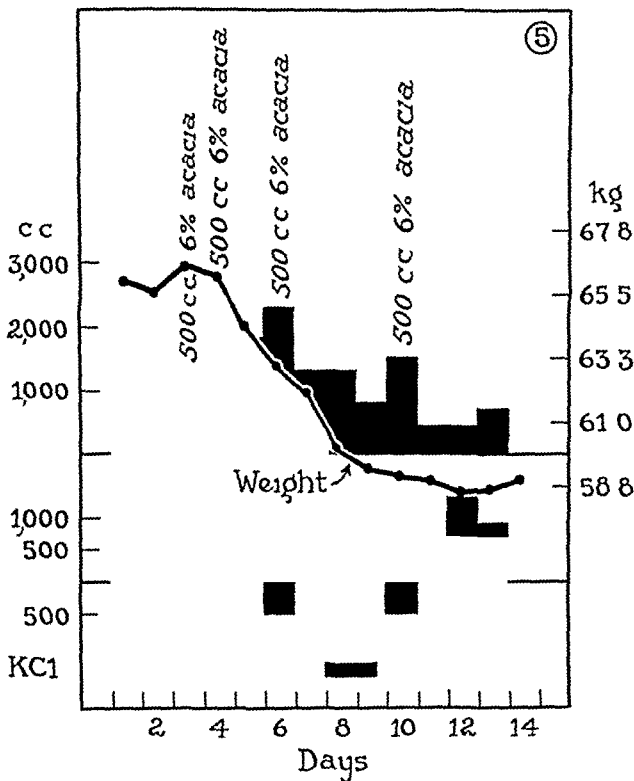


Chart 6 (case 5) —Essential factors of fluid balance in the case of a patient with nephrotic edema. The marked diuretic effect of acacia without simultaneous administration of potassium salts is obvious, the patient lost 135 pounds (61 Kg) in five days. Additional loss of 25 pounds (11 Kg) made the patient entirely free of edema on dismissal from the hospital. The details of the chart are explained in the legend of chart 1.

puffiness of the eyelids was noted, the second aortic sound was accentuated, ascites (grade 1 to 2) was present, and rather extensive edema of the lower extremities was noted. The ocular fundi showed extensive retinitis of the acute angiospastic type, with a great deal of "cotton-wool" exudate, hemorrhages and some edema, a condition similar to the angiospastic retinitis associated with chronic glomerulonephritis. The urine had a specific gravity of 1.028 and contained albumin, grade 4, casts, grade 3, and erythrocytes, grade 1. The concentration of urea was 69 mg, that of cholesterol, 536 mg, and that of serum proteins, 3.7 Gm, per

hundred cubic centimeters of blood. The albumin-globulin ratio was 1:12 and the colloid osmotic pressure of the serum was 73 mm of water. A diagnosis of chronic glomerulonephritis with nephrotic features and superimposed diffuse arteriolar disease with hypertension was made. After treatment in the hospital (chart 7), during which the colloid osmotic pressure of the serum rose to 114 mm of water, he was dismissed, with only a slight residual edema, on the twenty-fifth day of hospitalization and was advised to continue the hospital regimen. He was last heard from July 22, at which time he stated that he had lost 6 pounds (2.7 Kg.) after leaving the hospital, and that he was feeling very well and doing a limited amount of work without noticing any ill effects.

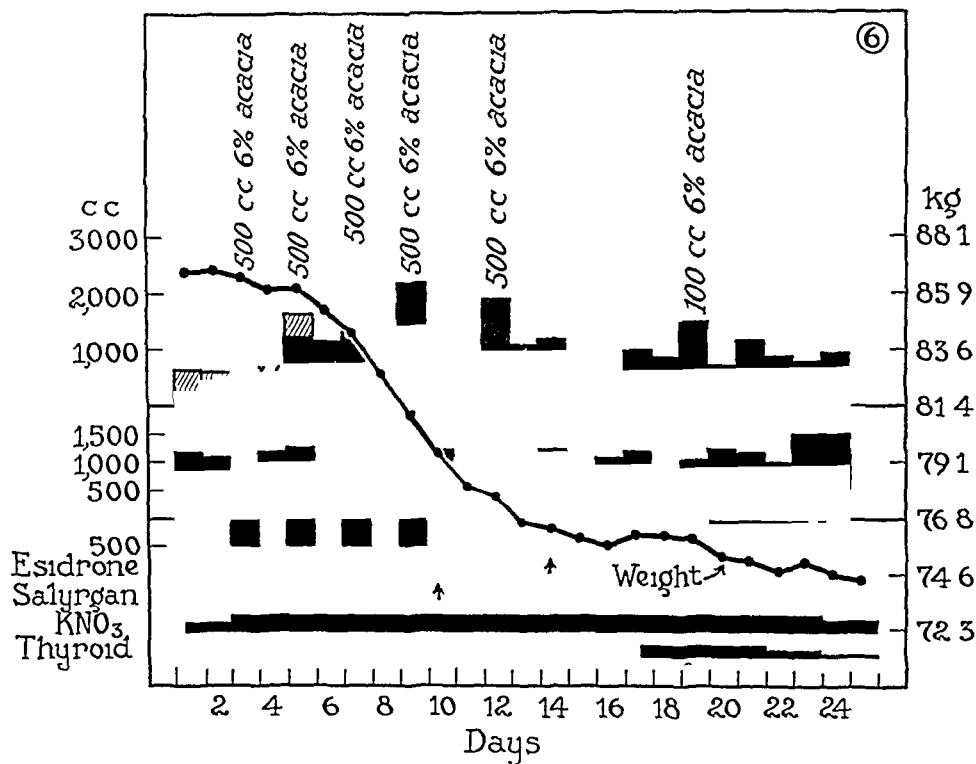


Chart 7—Essential factors of fluid balance in the case of a patient with nephrotic edema, treated by the standard regimen in the hospital. The patient received potassium nitrate, 10 Gm in the first two days combined and then 12 Gm per day until the last two days, when the dose was 8 Gm daily, and, desiccated thyroid gland, starting on the seventeenth day, $4\frac{1}{2}$ grains (0.29 Gm) daily, the dose being soon reduced to 3 grains (0.2 Gm) and $1\frac{1}{2}$ grains (0.1 Gm) respectively. Neither salyrgan (1 cc) nor esidrone (1 cc) was followed by an appreciable diuretic response. The chart illustrates how each injection of acacia was followed by a definite diuretic response, while the dietetic treatment and the amount of potassium nitrate given daily remained essentially constant throughout the period of hospitalization. The details of the chart are explained in the legend of chart 1. The cross-hatched blocks on top of those that represent the volume of urine indicate the volume of output by emesis.

The increased output of urine following each injection of acacia is remarkable and, in view of the constancy of the other therapeutic measures, points definitely to the beneficial properties of acacia itself.

Mercurial diuretics did not appear to increase the rate of disappearance of edema under the regimen employed

In the following 3 cases the edema was of multiple origin Acacia was employed in the treatment

CASE 7—A woman 53 years of age was known to have had chronic glomerulonephritis for many years and renal insufficiency for some years In addition, she was suffering from myocardial degeneration and insufficiency, which had been responsible for keeping her in bed most of the time for the past few years In addition, at the time of admission to the hospital (in September 1938) secondary diffuse arteriolar disease with hypertension was developing She had albuminuria grade 4 The concentration of urea was 84 mg, that of cholesterol, 315 mg, and that of serum proteins 4.7 Gm, per hundred cubic centimeters of blood The albumin-globulin ratio was 1.9:1, and the colloid osmotic pressure of the serum was 149 mm of water The blood urea clearance was 30.6 cc per minute at a volume of 170 cc At home the patient had been treated for a long time with digitalis and potassium nitrate in addition to being placed on a salt-free diet and permitted a limited intake of fluids However, a moderate amount of edema was present on admission After treatment with acacia (90 Gm in five days) she became free of gross evidence of edema, and the colloid osmotic pressure of the serum increased to 161 mm of water

In view of the other treatment administered, which consisted of administration of digitalis, aminophylline and potassium nitrate, it is difficult to evaluate the exact role which the acacia played in clinical recovery of the patient However, it would appear that the increased colloid osmotic pressure would have facilitated the flow of fluid from the tissues to the blood It is especially noteworthy that the blood pressure, measured before breakfast every morning, did not increase after the use of acacia Equally remarkable is the fact that, although part of the patient's edema was clearly due to myocardial insufficiency, undesirable effects from the increase in blood volume which always follows the administration of acacia were not noted

CASE 8—A man 59 years of age was suffering from diffuse arteriolar disease with hypertension group 3 (according to the classification of Keith, Wagener and Barker²¹), coronary sclerosis, generalized arteriosclerosis, myocardial degeneration and decompensation and chronic glomerulonephritis with nephrotic features Albuminuria, grade 4, was present The concentration of urea was 38 mg, that of cholesterol, 321 mg, and that of serum proteins, 4.1 Gm, per hundred cubic centimeters of blood The albumin-globulin ratio was 1.1:1, and the colloid osmotic pressure of the serum was 88 mm of water The patient was treated in the hospital with the standard diet, fluids were restricted, and 9 Gm of potassium nitrate was administered daily In addition to this, 1 cc of salyrgan was given on two different days, with only slight diuretic effect, so that in nine days in the hospital the patient had lost only 3 pounds (1.3 Kg) At this time

²¹ Keith, N M, Wagener, H P, and Barker, N W Some Different Types of Essential Hypertension Their Course and Prognosis *Am J M Sc* 197 332-343 (March) 1939

acacia was administered, a total of 84 Gm in five days. He lost 8 pounds (3.6 Kg) in the next five days, and at the end of this period was clinically free of edema. Salyrgan had not been used since the treatment with acacia had been started, and digitalis had not been employed during the entire period of hospitalization. The patient was dismissed from the hospital without edema.

Again it appears that although myocardial insufficiency was present, acacia had a definite part in relieving the patient's edematous state. The severe albuminuria, the low concentration of serum proteins, the inversion of the albumin-globulin ratio and the low colloid osmotic pressure leave little doubt that the patient, in addition to diffuse arteriolar disease with hypertension, was suffering from a nephrotic type of lesion and that part of the edema was due to the latter condition. Certainly the patient responded much better to acacia than to salyrgan, although treatment otherwise remained unchanged, which in turn possibly might be considered an indication of the nephrotic origin of the edema.

CASE 9—A man aged 27 had undergone splenectomy in 1931 because of splenic anemia, he had been in good health after the operation. In January 1937, after a severe attack of influenza accompanied by a sore throat, on getting out of bed he had noticed that his ankles were swollen. At that time much albumin and some erythrocytes were found in the urine. On admission to the clinic (December 12) physical examination gave essentially negative results except for a slight but definitely noticeable amount of ascites, considerable edema of the legs and some edema over the sacrum. The concentration of urea was 28 mg, that of cholesterol, 641 mg, and that of serum proteins, 5.3 Gm, per hundred cubic centimeters of blood. The albumin-globulin ratio was 1:1.4, and the colloid osmotic pressure of the serum was 147 mm of water. The blood urea clearance was 43.3 cc per minute at a volume of 32 cc per hour. Hepatic function, according to the results of galactose tolerance, hippuric acid and dye retention tests, was normal. The patient was given the standard treatment with potassium nitrate and acacia, and he lost 14.2 pounds (6.5 Kg) in eight days. He was dismissed from the hospital free of edema.

When the patient returned for reexamination, in October 1938, he again had some edema, although the concentration of serum proteins had increased to 6.7 Gm per hundred cubic centimeters. At this time, a few prominent veins were noted on the abdomen. The colloid osmotic pressure of the serum was 211 mm of water. In February 1939 some degree of ascites and dependent edema, in part controlled by the dietary measures, was present. Never during the course of his illness was any accumulation of fluid above the diaphragm noticed.

In this case, the concentration of serum proteins and the colloid osmotic pressure were never very low, and even after they had increased the ascites and dependent edema could not be controlled at all times. In view of the related history and the presence of prominent veins over the abdomen, it was assumed that some degree of obstruction of the portal circulation, possibly in combination with obstruction of flow in the inferior vena cava, had taken place. Thus, probably the edema ever since it first appeared had been of mixed origin. Nevertheless, response to acacia was prompt and satisfactory.

ACACIA IN THE NEPHROTIC SYNDROME WITHOUT EDEMA

As has been stated earlier in this study, patients in whose cases the laboratory data denote the nephrotic syndrome may or may not have actually manifest edema. Some may have only slight degrees of edema which may be controlled with diet alone or with diet supplemented by interrupted courses of potassium or ammonium salts. Usually the colloid osmotic pressure, although decreased, is not as greatly reduced as in cases in which severe degrees of edema exist.

In the last two years at the Mayo Clinic, acacia has been administered to 10 patients who had the nephrotic syndrome but practically no edema. Since edema was not present, it is difficult to judge the success of what might be called "prophylactic" treatment with acacia. One of the objects of this treatment has been to enable patients who have a tendency toward formation of edema, decreased renal function and retention of urea in the blood to take somewhat larger amounts of fluid than is customary. In a number of instances we have seen definite decreases in the concentration of blood urea following the use of acacia. Some patients without renal insufficiency have indicated that they could tolerate a larger intake of fluid after injection of urea in the blood or on the blood pressure. However, more experience is necessary before a final opinion can be expressed about the merits of administration of acacia to patients who have the nephrotic syndrome without edema.

LIMITATIONS OF EFFECTIVENESS OF COMBINED THERAPY

In 4 of a total of 40 cases the combined form of treatment proposed did not lead to satisfactory diuresis. In addition, 3 patients who at one time responded well were not controlled satisfactorily during a relapse. One of these, readmitted to the hospital a few weeks later, lost edema rather promptly. The case of this patient is especially interesting in that at the time of the first admission the colloid osmotic pressure of the serum was 145 mm of water, and when treatment was effective again, it was 116 mm. Nevertheless, in 1 case in which the edema was rapidly relieved the colloid osmotic pressure of the serum before treatment with acacia was only 62 mm of water, and even after completion of the course of injections of acacia it increased only to 67 mm.

In reviewing the cases in which treatment for reduction of edema was unsuccessful, we find that there are several probable causes of failure. They include (1) anorexia and vomiting, (2) insufficient amounts of diuretic salts and (3) insufficient amounts of acacia.

The cause of the anorexia and vomiting occasionally observed in patients with nephrotic edema is not well understood at present. Exam-

inations of the gastrointestinal tract in these cases, as well as tests of hepatic function gave negative results throughout. In this respect the condition in these cases may be thought to simulate anorexia nervosa and nervous vomiting. However, the symptoms are more likely to be secondary to the renal disease itself. The reduced intake of food results in malnutrition, and a vicious cycle is thus established. Resolution of the edema is further hampered by inability to ingest the necessary amounts of diuretic salts. The seriousness of the condition is illustrated well by the fact that of the 4 patients 3 are known to have died since their dismissal from the hospital, and we have not been able to reestablish contact with the fourth. The most rational attack on the problem might well incorporate parenteral administration of all nutritional and therapeutic materials which are not tolerated by mouth. The need for treatment of patients with this condition is all the more urgent because it is known that once they have been liberated of edema appetite returns, morale improves and the vicious cycle is broken.

Diuretic salts should be given in all cases for a sufficient period and in sufficient dosage. Their administration for two or three days should precede injection of acacia if one is to expect optimal results. Premature discontinuance in the occasional case definitely jeopardizes the ultimate success of the combined form of treatment.

In many cases of the severe types of nephrotic edema much acacia is lost in the urine, and it is difficult to reach an optimal concentration in the body. The dosage of acacia, at present, is mostly on an empiric basis. Thus, in rare cases larger doses than those recommended in this paper may well be necessary.

COMMENT

General Considerations—The nephrotic syndrome is characterized by albuminuria, hypercholesteremia, a low concentration of serum proteins and a low colloid osmotic pressure of the serum. The last two factors generally are considered directly responsible for the edema, without which the syndrome is usually asymptomatic. The composition of the edema fluid, which contains only a small amount of protein, corresponds closely to an ultrafiltrate of serum, being essentially an isotonic solution of sodium chloride and other ions. It accumulates in excess in the tissue spaces.

The large amount of albumin excreted in the urine is derived from the proteins of the serum, largely from the albumin fraction, and this constant drain is considered the main reason for the diminished amounts of protein found in the serum. Starling,²² in 1896, published his experi-

22 Starling, E. H. On the Absorption of Fluids from the Connective Tissue Spaces, *J. Physiol.* **19** 312-326, 1896.

ments on the rate of absorption of fluid from the subcutaneous tissues. He found that salt solutions were much more readily absorbed than were those containing proteins. This has led to our present conceptions of the exchange of fluid through the capillary membrane, the amount of fluid filtered through depending on the relation between the intravascular hydrostatic pressure, which tends to force fluid from the capillaries into the tissue spaces, and the colloid osmotic pressure of the serum proteins, which attracts fluids from the tissue spaces toward the lumens of the blood vessels. In accordance with this scheme, in conditions of hypoproteinemia and low colloid osmotic pressure of the serum the normal dynamic equilibrium will be displaced, so that a larger amount of fluid is expressed from the lumen toward the tissue spaces than is reabsorbed, and edema appears.

This mechanical conception loses its applicability as soon as the role of the kidney in the syndrome is studied. With oliguria as an essential part of the nephrotic edematous state, apparently the diminished water-binding power of the blood proteins does not make for an increased final volume of transudate (urine). Formerly, it was thought that the edema "deviated" fluid from the processes of urine formation (so-called prerenal deviation). But that conception is not in accordance with the newer views of renal function, which postulate for man a rate of glomerular filtration of the order of 150 cc per minute, this value presumably is approximately as large in the true nephrotic state as it is in the normal, as is evidenced by the normal results of clearance tests in those cases of chronic nephrosis in which glomerulonephritic changes are absent.

No satisfactory explanation appears to exist at present for the small volume of urine with high specific gravity and low chloride content which is so characteristic of the edematous nephrotic state. However, the same situation presumably is encountered in cases of so-called nutritional edema and in cases of edema of undetermined origin, such as have been described by Binger and Keith²³. An analogous state also may be produced in animals by the use of repeated plasmapheresis. The weight increases, and visible edema develops, presumably because water and salt are not excreted in sufficiently large quantities. The volume of urine is decreased even more if sodium chloride is administered orally at the same time.

Thus, in view of the analogous situation encountered among patients who have the nephrotic syndrome and other conditions of hypoproteinemic edema and in animals subjected to plasmapheresis, it appears that failure of the kidney to excrete water and sodium chloride in sufficient

23 Binger, M. W., and Keith, N. M. General Edema of Indeterminate Etiology. Report of Three Cases, *J. A. M. A.* **109** 1-6 (July 3) 1937.

amounts is conditioned by decrease of the concentration of serum proteins or of the colloid osmotic pressure of the serum. This failure on the part of the kidney is only relative, since satisfactory diuresis often can be obtained without simultaneous increases of the colloid osmotic pressure of the serum. Such diuresis may be induced by a change in the ionic environment, such as occurs with the administration of potassium nitrate, or by a forceful change of tubular permeability, such as is effected by administration of mercurial diuretics or such as may occur during so-called spontaneous diuresis when the patient is maintained on a salt-free regimen.

On recognition of decrease of the colloid osmotic pressure of the serum as conducive to the development of edema (1) through the understandable mechanism of increased filtration and decreased reabsorption through the wall of the capillaries in the body at large, and (2) through the less well understood phenomenon of decreased elimination of chloride and water by the kidney, it appears imperative to foster attempts to remedy this deficiency. Four different types of treatment are usually employed, often more than one at the same time: a high protein diet, blood transfusion, administration of concentrated lyophil serum and injection of acacia.

At present, administration of a high protein diet is part of the generally accepted method of treatment of the nephrotic syndrome and should be utilized regardless of what other forms of treatment are being used. The futility of transfusions to bring about an increase in colloidal osmotic pressure of the serum is clear when it is realized that such procedures add to the blood stream an amount of protein equal to the amount which is being excreted every one to seven days in the urine in the type of case under consideration.

The first observations on the use of concentrated lyophil serum, published by Aldrich and his co-workers,²⁴ appear favorable. The amounts of serum proteins given exceed the ones present in the average transfusion, and the results appear definitely superior. Further experience with this form of treatment is being awaited with great interest, especially since an instance of very rapid and complete cure is cited in the original communication.

The administration of acacia may produce a temporary rise in the colloid osmotic pressure of the serum (Kerkhoff, Butt, Power and Keys, Peters). The substance remains within the circulation for extensive periods, although not as long in cases of nephrosis as in cases in which albuminuria is not present. These and other problems bearing

24 Aldrich, C. A., Stokes, J., Killingsworth, W. P., and McGuinness, A. C. Concentrated Human Blood Serum as a Diuretic in the Treatment of Nephrosis. Preliminary Report, *J. A. M. A.* **111** 129-133 (July 9) 1938.

on the mechanism whereby acacia exerts its favorable therapeutic effect are being investigated at present and will be reported on later

Clinical Considerations—Clinically the results of treatment of nephrotic edema with acacia are highly satisfactory. Used in conjunction with a high protein, salt-free diet, restriction of fluid and administration of potassium nitrate, disappearance of the edema at a rate averaging between 1 and 3 pounds (0.5 and 1.3 Kg) per day could be observed in 36 cases. The patients subsequently could be dismissed from the hospital free of edema or practically so. Of 40 consecutive patients hospitalized for treatment of a nephrotic type of edema, to whom acacia was administered when they were first admitted to the hospital, the treatment afforded efficient loss of edema in 36 (90 per cent). These figures cannot be compared with any others in the literature, because a comprehensive analysis of therapeutic results in a consecutive series of cases of nephrotic edema has not been published. The absence of such a study explains the vague and subjective presentation of the therapeutics of the nephrotic type of edema usually encountered.

A review of 7 cases in which, at one time or another, there was failure to respond to the described regimen of diuretic therapy revealed that in the majority of instances great difficulty had been encountered in having the patients take their diet and diuretic salts. In practically all cases potassium nitrate had not been given in the full therapeutic dose or over a sufficiently long period. Future advances in the treatment of nephrotic edema may well be centered in finding some modification of the present regimen which would not depend on the oral route for administration of nutritional and therapeutic essentials. However, it should be realized that probably no form or combination of treatments will ever be effective and successful in 100 per cent of cases.

Safety of Injections of Acacia—Acacia can be given with comparative safety, and when it is used in combination with the other component parts of the recommended regimen its effective dose is so low that toxic effects from overdosage are not observed. Thus, administering a total amount of approximately 15 to 2 Gm per kilogram of body weight in the course of three to six days has never given rise in our experience to enlargement of the liver, although we have been watching for it diligently. We have thought it advisable to refrain from repeating the course of treatment with acacia until a sufficient period had elapsed. Thus, in order to obtain the maximal benefit, one would do well to precede the injections of acacia by two or three days' treatment with diuretic salts.

In connection with the alleged damage to the liver, it is worth remembering that all of those investigators who have stressed this point

most used doses many times larger than those mentioned and recommended in the present study Butt and Snell²⁵ found that acacia, the same preparation that we have used, in approximately the same dosage, is well tolerated by patients who have cirrhosis of the liver with ascites and that it does not provoke the appearance of clinical signs or symptoms suggestive of further impairment of hepatic function These observations furnish additional valuable clinical evidence that under the regimen of treatment recommended acacia does not exert any harmful effect on the liver

The decrease in concentration of serum proteins which is regularly observed after injections of acacia and which by some investigators is ascribed to damage of the liver can be explained most simply on the basis of dilution of the serum with the colloidal solution of acacia, certainly the decreases in values for serum protein on the one hand and in those for hemoglobin and hematocrit values on the other, such as are observed after a course of injections of acacia, are of comparable magnitude Also, the decrease in concentration of serum proteins is greatest shortly after the injection of acacia, and a definite tendency toward an increase is noticeable from that time on Such behavior does not appear to be compatible with the idea of hepatic dysfunction as the cause of the decrease in the concentration of serum proteins

Thus, acacia is an effective therapeutic agent and is harmless if certain principles of preparation and administration are adhered to Its inclusion in the regimen of the adult patient who has nephrotic edema, in addition to the usual dietary measures, and administration of diuretic salts in the great majority of instances give prompt and satisfactory results

SUMMARY

Acacia can be incorporated advantageously into the regimen of treatment of the patient who has a nephrotic type of edema Other therapeutic features should include the use of a salt-free, high protein diet, the restriction of fluids and the use of diuretic salts, preferably potassium nitrate Of 40 successive adult patients treated according to these principles, all except 4 were promptly relieved of edema Most often, failure of the treatment was due to inability of the patient to take sufficient nourishment and diuretic salts by mouth

Diuretic salts are not essential, for acacia may produce diuresis when used in conjunction with diet alone The best results, however, are most likely to be obtained if diuretic salts are included in the regimen

Additional diuretic measures are seldom called for Thus, except in a few instances, mercurial diuretics can well be dispensed with without

25 Butt, H R, and Snell, A M Personal communication to the authors

sacrifice of therapeutic results. Sometimes diuretics ineffective before treatment with acacia become effective after such treatment.

Once proper attention is given to the preparation and administration of acacia, reactions after its injection are infrequent and mild. The dosage is important, the amount given in each course of treatment should be limited to 90 to 150 Gm. divided in daily doses of 30 Gm. Enlargement of the liver has not been observed at any time. In this fashion acacia may even be given to patients who have cirrhosis of the liver without further impairing hepatic function. The decrease in serum proteins observed after its injection can be accounted for adequately on the basis of increase in plasma volume and concomitant dilution of its constituents. Neither renal insufficiency, secondary vascular disease nor myocardial degeneration constitutes a contraindication to its use.

Thus, the addition of injections of acacia to a general regimen of treatment appears to provide efficient results for the patient who has a nephrotic type of edema.

CEREBRAL ABSCESS (PARADOXIC) ACCOMPANYING CONGENITAL HEART DISEASE

REPORT OF TWO CASES

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Cerebral abscess occurring in patients with congenital disease of the heart is rare and not commonly recognized. There are early recorded observations of cerebral abscess in patients dying with congenital heart disease, but it was not until 1880 that Ballet¹ first made clear the relationship of these two morbid conditions.

The incidence of congenital heart disease varies considerably in the necropsy observations reported from different institutions. For example, 75 cases of this anomaly reported by Leech² from the Johns Hopkins Hospital constituted 129 per cent of all the cases in which necropsy was done, whereas the 105 cases of congenital anomalies of the heart or the great vessels reported by Gibson³ from the cardiac service of the Children's Memorial Hospital were 54 per cent of the 1,950 cases of infants on whom autopsy was performed. Cerebral abscess as a complication is not mentioned by either author. All the patients seem to have died from cardiac disease.

The term "paradoxical embolism" seems first to have been suggested by von Recklinghausen. Gowers⁴ spoke of 2 or 3 cases of abscess of the brain in association with congenital heart disease. In 1912 Osler⁵ stated that death of patients with congenital heart disease may be

From the Neurological and Neurosurgical Service of the Mount Sinai Hospital

1 Ballet, G. Des absces du cerveau consécutifs à certaines malformations cardiaques, *Arch gen de med* **5** 659, 1880

2 Leech, C B. Congenital Heart Disease. Clinical Analysis of Seventy-Five Cases from Johns Hopkins Hospital, *J Pediat* **7** 808-839 (Dec) 1935

3 Gibson, S., and Clifton, W M. Congenital Heart Disease. Clinical and Postmortem Study of One Hundred and Five Cases, *Am J Dis Child* **55** 761-767 (April) 1938

4 Gowers, W R. A Manual of Diseases of the Nervous System, London, J & A Churchill, 1888, vol 2, p 443

5 Osler, W. The Principles and Practice of Medicine, ed 8, New York, D Appleton and Company, 1912

caused by abscess of the brain. In 1923 Abbott, Lewis and Beattie⁶ collected 14 cases of paradoxical embolism. Six of these proved to be cases of cerebral abscess. Abbott's⁷ study of 1,000 cases of congenital heart disease with associated patency of the foramen ovale, interventricular septum and ductus arteriosus contained 12 cases in which death occurred as the direct result of paradoxical embolism.

Four additional cases were found in the literature by Rabinowitz, Weinstein and Marcus,⁸ and they reported 1 in which the abscess at autopsy was found in the cerebellum. Seven cases of paradoxical embolism observed at the Mayo Clinic were reported by Ingham,⁹ in all of which the condition was associated with patent foramen ovale and preceded by pulmonary embolism. It is interesting that in 1 of these cases the patient presented sufficient localizing signs to warrant exploration of the left temporoparietal lobe for a cerebral abscess. Death followed on the thirteenth postoperative day. To our knowledge this is the first recorded case in which an attempt was made to drain a cerebral abscess following paradoxical embolism.

There is no adequate explanation of the mechanism of the production of "paradoxical" cerebral abscess accompanying congenital disease of the heart. In some cases there was a history of antecedent infection. For example, in cases 2 and 3 reported by Abbott, Lewis and Beattie there was evidence of an inflammatory focus shortly before the onset of the cerebral symptoms. In the case reported by Bach¹⁰ the removal of carious teeth seemed to be the spark that started the symptoms. In the case reported by Ingham there was an infection of the upper respiratory tract three days before the onset of neurologic symptoms. Baumgartner and Abbott¹¹ were unable to locate the focus in their case of paradoxical embolism with cerebral abscess, yet they felt that sepsis in the lesser circulation must have been present. They stated the opinion that cerebral

6 Abbott, M. E., Lewis, D. S., and Beattie, W. W. Differential Study of a Case of Pulmonary Stenosis of Inflammatory Origin (Ventricular Septum Closed) and Two Cases of (a) Pulmonary Stenosis, and (b) Pulmonary Atresia with Associated Ventricular Septal Defect and Death from Paradoxical Cerebral Embolism, *Am J M Sc* **165** 636-659 (May) 1923.

7 Abbott, M. E. Congenital Heart Disease, in Nelson's New Loose-Leaf Living Medicine, New York, Thomas Nelson & Sons, 1927, vol. 4, pp. 207-321.

8 Rabinowitz, M. A., Weinstein, J., and Marcus, I. H. Brain Abscess (Paradoxical) in Congenital Heart Disease, *Am Heart J* **7** 790-795 (Aug.) 1932.

9 Ingham, D. W. Paradoxical Embolism, (with Patent Foramen Ovale), *Am J M Sc* **196** 201-207 (Aug.) 1938.

10 Bach, F. A Case of Congenital Morbus Cordis Studied Over a Period of Twelve Years, *Lancet* **1** 1009-1011 (May 19) 1928.

11 Baumgartner, E. A., and Abbott, M. E. Interventricular Septal Defect with Dextroposition of Aorta and Dilatation of the Pulmonary Artery ("Eisenmenger Complex") Terminating by Cerebral Abscess, *Am J M Sc* **177** 639-647 (May) 1929.

abscess is especially liable to occur when there is a defect in the ventricular septum as well as a dextroposition of the aorta. This combination seems to favor a direct path for the transmission of a crossed embolus. Another possible explanation is that vascular disease of the

*Outstanding Findings in Reported Cases of Cerebral Abscess Associated
With Congenital Heart Disease*

Author	Age, Years, and Sex	Symptoms	Signs	Duration of Illness	Location of Abscess
Ferre, J. R.	9½ M	Headache, fever	Left hemi- plegia	4 days	Right hemisphere
Bertody, Charles	21 F	Headache, delirium, fever, coma			Left posterior hemi- sphere and left ventricle
Stone, W. H.	19 F				Right occipital lobe, right ventricle
Deneke, T.	18 M	Headache	Left hemi- plegia	10 days	Right cerebral hemi- sphere, streptococci
Abbott, Lewis and Beattie	11 M	Headache, fever	Right hemi- plegia	2 days	Left frontal lobe, puru- lent meningitis
Riab, William	15 M	Headache, fever	Left hemi- plegia	3 weeks	Right hemisphere, puru- lent meningitis
Bach, Frances	30 M	Headache, fever, coma		1 day	Right temporal lobe purulent meningitis
Baumgartner and Abbott	20 M	Headache, drowsiness, coma	Papilledema, left hemiplegia, left facial weak- ness, increased spinal fluid pres- sure, 9 cells	17 days	Right frontoparietal area, 5 cm. in diameter
Ballet, G.	15 M		Left hemi- plegia	10 days	Frontal lobe, purulent meningitis
Lullenand	57 F		Left hemi- plegia	10 days	Frontal lobe, purulent meningitis
Rabinowitz and others	16½ F	Fever, headache vomiting		7 days	Cerebellum
Ingham	39 F	Right side of face and right hand numb, twitch- ing right arm			Left hemisphere
Wechsler, I. S., and Kaplan, A. (present study)	14 M	Convulsion, headache, vomiting	Numbness on left side of body, papilledema, left facial paralysis and left hemi- paresis	64 days	Right parietal lobe
Wechsler, I. S., and Kaplan, A. (present study)	11½ F	Headache, convulsion	Left facial paralysis, left hemiplegia	43 days	Right frontal lobe

brain together with consequent encephalomalacia prepares a focus which is receptive to infection, and if by chance organisms circulate in the blood they may cause the formation of an abscess.

In previous reports on this subject stress has been placed on valvular and vascular defects and anomalies. Comparatively little attention has been focused on the cerebral complication. With the lesion in the brain localized, the diagnosis generally is thrombosis or embolism.

The object of this report is to recall the fact that unheralded cerebral abscess may occur in persons with congenital heart disease and to point out that the abscess, which generally is single, should be drained

In tabular form a review of the 12 collected cases from the literature of cerebral (paradoxical) abscess associated with congenital heart disease is presented. Particular note should be taken of the short duration of the illness, and also of the fact that the complication of cerebral (paradoxical) abscess is most frequent in those cases in which there are signs pointing to the tetralogy of Fallot. It is worth noting that 10 of the 14 abscesses occurred on the right side of the brain. Actually it is 10 out of 13, as 1 was in the cerebellum. What significance this has is difficult to say. One explanation which suggests itself is that the dextro-position of the aorta may in some way be responsible. This would be based on the assumption that an embolic process precedes the formation of the abscess.

REPORT OF CASES

CASE 1—D. G., a 14 year old school boy, was first admitted to the Jewish Hospital (Brooklyn) on July 25, 1935 because of convulsions of two weeks' duration.

The family history was irrelevant. At birth the patient was a "blue baby," and from the beginning he was recognized as having congenital cardiac disease. He had measles, mumps and chickenpox without complications. Two months before admission to the hospital he had an attack of influenza. He was guarded in his daily activities, and had advanced to high school.

Two weeks before admission he was suddenly seized with a convulsion which was regarded as an epileptic fit. Three days later he had another seizure, which involved the left side of the face, neck, arm and trunk, and he immediately lost consciousness. Shortly after the second convulsion he complained of pain in the right eye and numbness of the left side of the face and trunk. For nine days there were repeated episodes of headache and vomiting and increased drowsiness.

Examination—On admission the boy appeared acutely ill, with cyanotic lips and skin, moderate exophthalmos and typical clubbing of the fingers. There were a pronounced bulging of the pulmonary conus, an apical thrill during systole and a loud rough murmur over the entire precordium, most marked over the apex (tetralogy of Fallot). The blood pressure was 100 systolic and 70 diastolic, the temperature 99 F, the pulse rate 75 and the respiratory rate 22.

The positive neurologic findings were bilateral papilledema, more advanced on the right, ptosis of the right eyelid, hypesthesia of the left cornea, weakness of the left side of the face, left hemiparesis, more marked in the arm, absence of abdominal reflexes on the left side, and more active deep reflexes on the left side.

Laboratory Data The urine was normal. The blood count revealed hemoglobin, 91 per cent, erythrocytes, 8,750,000 per cubic millimeter, and leukocytes, 5,200 per cubic millimeter, with 73 per cent polymorphonuclear cells and 24 per cent lymphocytes. The blood sugar value was 106 mg, the creatinine content 1.4 mg, and the urea nitrogen content 10.8 mg per hundred cubic centimeters. Roentgen examination of the chest showed a broadened cardiac shadow of the left ventricular region, suggesting hypertrophy. Wassermann and Kahn tests of the blood

gave negative reactions. The electrocardiogram revealed dominant sinus rhythm, right axis deviation and auricular hypertrophy. The sedimentation rate was 8 mm in one hour. Examination of the spinal fluid revealed a pressure of 480 mm, no cells, a sugar content of 78 mg, 729 mg of chlorides per hundred cubic centimeters, and a total protein value of 33 mg per hundred cubic centimeters. No organisms were revealed by smear or culture.

Course—During the first week of observation the headaches subsided, vomiting became less frequent and drowsiness grew less marked. At times pain over the right eye became severe. The papilledema gradually increased. There was no evidence of an enlarged spleen, of petechiae or of positive results of blood culture. On the tenth day after admission the temperature was 100.6 F and the pulse rate 55, and the patient suddenly lost consciousness for five minutes. Ankle clonus and the Babinski sign on the left side were now present, but in addition the right arm became spastic and there was also a positive Babinski sign on the right.

Operation—Operation was performed on Aug 3, 1935, with the region under local procaine hydrochloride anesthesia, a trephination being done over the right parietal area. The exposed dura appeared normal and surprisingly, pulsated



Fig 1—*A*, aerogram showing position of the abscess cavity in the right parietal lobe (case 1), *B*, lateral view of the abscess cavity (case 1)

freely. A ventricle needle was inserted, and at a depth of 5 cm pus was obtained. Sixty cubic centimeters of pus was aspirated. A smear of the pus showed gram-negative bacilli and gram-negative diplococci. Cultures for aerobic and anaerobic organisms showed no growth. The day following the operation the patient was conscious. The right pupil was larger than the left. There was palsy of the left external rectus muscle, the neck was stiff, and there was a bilateral Kernig sign. The temperature was 101 F and the pulse rate 78. During the next two weeks the patient showed some improvement, the neck was less rigid, and there was some return of power in the left arm and leg. At times he vomited and complained of pain in the right eye. The temperature remained below 100 F for a week. However, the papilledema did not subside. Then the frontal headache and the pain in the right eye returned, nausea and vomiting increased and the patient complained of gustatory and olfactory hallucinations.

On Aug 19, 1935 at 2:30 a m, after a generalized convulsion, he lost consciousness and presented the picture of decerebrate rigidity. Aspiration through the trephine opening yielded 50 cc of pus. He regained consciousness shortly thereafter, the headaches disappeared, and he remained in a satisfactory state for

the next three days, when the headaches recurred, vomiting followed and the left hemiparesis became more pronounced. Aspiration through the trephine opening was repeated and 45 cc of pus removed. At this time 25 cc of air was injected. Roentgen examination of the skull (fig 1 *A* and *B*) showed a well rounded air pocket about 4 cm in diameter in the right parietal region.

Although the patient improved for two days after this procedure, the headaches and vomiting recurred and he appeared extremely ill. A more radical operation was decided on. On Aug 24, 1935 the wound and bone defect were enlarged, the dura coagulated at the bone margins, the brain incised and a Mosher drain inserted into the abscess cavity. For one week after this operation there was remarkable improvement, but then the headaches returned, the papilledema progressed and a bilateral Kernig sign and a Babinski sign on the left again became evident. Vomiting continued, the temperature rose to 101 F and the pulse rate to 120, and the paresis became more marked. The spinal fluid was cloudy and showed 4,000 leukocytes per cubic millimeter, with 84 per cent polymorphonuclears and 14 per cent lymphocytes. Two cultures of the blood yielded no growth. Repeated studies of the spinal fluid showed increase in pressure and pleocytosis, the cells being chiefly mononuclear, but no organisms were revealed by smear or culture. Clinically the patient presented the picture of meningitis with spreading encephalitis. He died fifty days after admission to the hospital. Necropsy was refused.

CASE 2—A school girl 11½ years of age was admitted to the Mount Sinai Hospital on March 31, 1939. At birth the child was recognized as a "blue baby" and was known to have congenital heart disease. During early childhood she had measles, chickenpox and whooping cough.

Three months before admission, for three weeks, she had cough and fever which were diagnosed as bronchitis. On March 27, 1939, four days before admission, she began to complain of headache in the right supraorbital region. This was the only symptom for three days, when she suddenly had typical jacksonian clonic convulsions of the entire left leg. There was no aura or loss of consciousness, the seizure lasted about one minute and was followed by weakness of the left leg. Several hours after this attack she had a second one, identical with the first. On the morning before admission to the hospital, weakness of the left arm also became apparent, and during the afternoon she had a third convulsion.

Examination—On admission, examination showed a tall thin girl, with blue lips and long, clubbed, cyanotic finger tips with curved nails. She complained of headache. The temperature was 102 F. and the pulse rate 96 and the respiratory rate 22 per minute. Examination of the heart showed congenital heart disease with the "tetralogy of Fallot." There was a systolic thrill over the third left interspace at the sternal margin. There was also a loud harsh systolic murmur, which was transmitted from this region over the entire precordium. The first sound at the apex was snapping, and the aortic second sound was louder than the pulmonic second sound. The systolic blood pressure was 100 and the diastolic 60. The electrocardiogram showed right axis deviation and high voltage, which are seen in patients with congenital heart disease. Roentgen films of the chest revealed moderate enlargement of the heart to the right, a widened arch and diminution in the size of the root of the left pulmonary artery. Roentgenograms of the skull showed the pineal shadow displaced to the left.

The neurologic findings were a weakness of the left side of the face, some spasticity of the left leg, positive Babinski and Chaddock signs on the left side and a transient ankle clonus on the left side.

Laboratory Data The urine was normal. The hemoglobin content of the blood was 110 per cent, with 6,100,000 red blood cells per cubic millimeter. The leukocytes numbered 15,000 per cubic millimeter, 66 per cent being polymorphonuclear cells and 28 per cent lymphocytes. The Wassermann reaction of the blood was negative. Blood culture showed no growth. The spinal fluid was under initial pressure, it gave a 4 plus reaction to the Pandy test and had 3 lymphocytes per cubic millimeter.

During the first four days after admission the patient continued to complain of frontal headache. There were a few nystagmoid jerks on right lateral gaze. The temperature ranged between 98 and 101 F and the pulse rate from 54 to 60. The right fundus became hyperemic. The left cornea became less sensitive and the neck slightly stiff. The abdominal reflexes could no longer be obtained. The patient became drowsy. The spinal fluid showed an initial pressure of 118 mm, the reaction to the Pandy test was 2 plus, and there were 25 lymphocytes per cubic millimeter. Thirty cubic centimeters of air was injected through the lumbar route but none appeared in either ventricle, there was some air over the left cortex

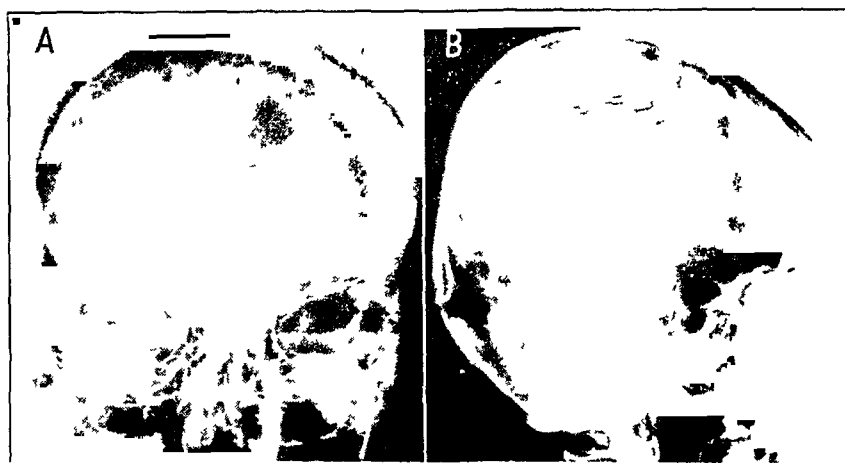


Fig 2—A, air in the abscess cavity (case 2), B, lateral view of the abscess cavity (case 2)

and in the basilar cistern. The increasing drowsiness, the bradycardia and the advancing papilledema pointed to an expanding intracranial lesion.

On April 8, with the area under local procaine hydrochloride anesthesia, a trephine opening was made in the right frontal region, about 1 inch (2.5 cm) from the midline. The exposed dura did not pulsate. At a depth of 4 cm a ventricle needle encountered brownish gray purulent material. Seventy cubic centimeters of foul-smelling matter was removed by aspiration and the wound closed without drainage. The pus on smear showed gram-positive cocci in pairs and in chains. Culture showed a growth of *Streptococcus viridans*. A. Sulfapyridine therapy was started.

After operation the patient became more alert and was no longer troubled with headache, but she complained of extreme nausea, which undoubtedly was due to the sulfapyridine. Within the next four days there was remarkable improvement. She showed more motion in the left leg and some movements of the fingers of the left hand, and she had only occasional headache. One week after the operation she suddenly cried out and became stuporous. Lumbar puncture was again per-

formed. The spinal fluid was under low pressure, 80 mm. It was clear and contained 9 lymphocytes. There was a 3 plus reaction to the Pandy test and the sugar content was 70 mg per hundred cubic centimeters. The patient regained consciousness after the lumbar puncture. Aspiration through the previous trephine opening yielded 30 cc of much thicker yellow pus. The sulfanilamide content of the pus was 8.3 mg per hundred cubic centimeters, as compared with 9.5 mg in the blood.

The following day the patient was again drowsy. Forty cubic centimeters of pus was aspirated, this time through the previous trephine opening and 25 cc of air injected. Roentgenograms of the skull (fig 2 *A* and *B*) showed a cavity 1 by 1½ inches (2.5 by 3.8 cm) in the right parietal region.

On April 18 a second operation was performed, with the patient under nitrogen monoxide-oxygen anesthesia. The previous wound was reopened, the bone defect enlarged to the size of a quarter, the dura sealed off with a coagulating current and the brain incised. At a depth of 3 cm a firm capsule was seen. A rubber tube drain was inserted. There was an escape of about 30 to 40 cc of thick pus.

Although the patient became more alert, the headaches continued, the fever took on a septic character, the neck became stiff and the left hemiparesis became worse. She became stuporous, and died forty-three days after the onset of symptoms and thirty days after operation.

SUMMARY

The 2 cases of cerebral abscess are reported, first, because of the rarity of the condition and, second, because early recognition may possibly lead to successful surgical relief. Altogether, 12 cases have been reported in the literature, and the 2 additional ones bring the total to date up to 14. In only 3, including our own 2, was the condition diagnosed during life and therefore treated surgically, in the rest the anomaly was not even suspected. As a rule a diagnosis of embolism or thrombosis is made. The rapidity with which the abscess generally forms justifies in some measure such a diagnosis. But the presence of fever, of leukocytosis, possibly of slow pulse and of early fundus changes should draw attention to the presence of an expanding intracranial lesion, more particularly an abscess. In cases in which the diagnosis is doubtful, pneumoencephalographic examination may be indicated. The important point to bear in mind is that abscess of the brain, though rare, can occur in patients with congenital heart disease, even though a primary focus of infection may not be detected. In any event early recognition as well as familiarity with the complication and with the underlying pathologic changes may lead to more successful surgical intervention.

PNEUMOCOCCIC PNEUMONIA

ANALYSIS OF THE RECORDS OF 1,469 PATIENTS TREATED IN THE
LOS ANGELES COUNTY HOSPITAL FROM 1934 THROUGH 1938

I CHARACTER OF PNEUMONIA CAUSED BY THE VARIOUS TYPES OF
PNEUMOCOCCI, COMPLICATIONS, OUTCOME OF PNEUMONIA IN THE
PRESENCE OF CERTAIN VARIATIONS IN THE PATIENT
AND IN THE COURSE OF THE DISEASE

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LOS ANGELES

Pneumococcic pneumonia is highly variable in causation, pathologic aspects, course and outcome. A clear knowledge of the range and significance of its variations is requisite to an adequate concept of the disease, to intelligent management of the patient and to any interpretation of the results of treatment. In this and the two succeeding papers are published the results of a study of the records of 1,469 patients with pneumococcic pneumonia. This paper is concerned with the development, course and outcome of the disease caused by the various types of pneumococci, with the complications of pneumonia and with alterations in the outcome attending certain variations in the patient and in the course of the disease. The second paper will deal with the character of the disease in the presence of associated or concomitant conditions and the third with the results of serum therapy.

MATERIAL AND METHODS

During the five year period from 1934 through 1938, about 10,000 patients with certain or probable "primary" or "secondary" pneumonia were treated in the Los Angeles County Hospital. Pneumococci were recovered in approximately 1,600 of the cases, the cause not being investigated in most of the others. By

This study was aided by the Pneumonia Fund of the School of Medicine, University of Southern California.

From the Department of Medicine, School of Medicine, University of Southern California, and from the Los Angeles County Hospital.

some of the workers detailed abstracts were prepared of the entire clinical nursing and laboratory record of each patient from whom pneumococci were recovered. One of the workers checked the abstracts with the original records prepared the data for tabulation and supervised the analysis. When there was disagreement in clinical notations the reviewer weighed the data in favor of the more experienced observer. When clinical and roentgen evidence were in persistent disagreement, the clinical evidence was accepted, most frequently the discrepancy was temporary and did not involve the reviewer's discretion. In some cases in which pneumococci were recovered the presence of pneumonia was ruled out, and in others two or more types were recovered during a single illness the records of such cases were discarded. The patients in the remaining cases whose records form the basis of these papers numbered 1-59 and all of them had clear evidence of pneumonia due to a single type of pneumococcus. It must be emphasized that the study was planned in the latter part of 1938 and has therefore been conducted on completed hospital records which were prepared without particular attention to the possibility of a survey; they were not systematized as to collection or recording of information and experimental methods were not used.

Until the latter part of 1936, types I, II and III were determined by precipitation methods "group IV" of our series including all pneumococci recovered but not typed. Since then the Neufeld method has been used to determine all of the Cooper types, and the term "group IV" was abandoned. Direct examinations of sputum were used rather than the method of mouse passage. Although cultures of the body fluids were not routinely made¹ they were helpful in establishing or confirming the cause. No review of physical findings is published in these papers but only the final diagnosis. The term "atypical" is used to indicate disease with distinctly atypical history, findings and course and "lobar" to indicate lesions not definitely atypical. (When all clinical evidence pointed to one or the other diagnosis, that diagnosis was retained in this report even if contradicted by observations at autopsy, only if there was some doubt ante mortem did the autopsy observations influence the diagnosis as reported in these papers.) All patients who died are included under the heading "death" whether they died from pneumonia with or without complications, from complication persisting after cure of the pneumonia or from an accident during pneumonia or its sequelae. The term "complication" includes all complications except bacteremia referable to the local pathologic process or to dissemination of the pneumococci (small pleural exudates discoverable only by roentgen examination or autopsy were disregarded). Survival without complication is called "optimum outcome," publication of that rate being necessary for the calculation of the overlap between the "mortality" and the "complication" rate, this overlap occurs because patients who die with complications are recorded under "death" and also under "complication." Simple statement of mortality and complication rates is ambiguous. If 50 per cent died and 50 per cent had complications, it is possible, depending on the degree of overlap, that all the patients had an unfortunate outcome or that half survived without complication. The per cent of all patients who died with complications is obtained by subtracting 100 from the sum of the three rates.

The data are summarized in tables, the written text being reserved for those aspects which appeared most interesting. The literature on these subjects is so voluminous that adequate references cannot be cited with brevity.

1 Laboratory facilities during the time covered by this report did not permit routine blood cultures.

RESULTS

The incidence of the types each year and for the five year period, as well as the annual incidence of pneumococcic pneumonia, are recorded in table 1. The apparent increase in pneumococcic pneumonia probably reflects an increase in effort to determine type rather than a true increase in incidence of the disease. Types I, II and III were responsible for less than half the infections, occurring in 42 per cent of the 1,469 patients—an incidence considerably less than that usually reported for the north Atlantic seaboard. The order of frequency of the Cooper types could be determined only for 1937 and 1938, the ten most frequent types being types I, VII, III, VIII, II, V, IV, IX, VI and XIV.

TABLE 1—*Distribution (per Cent) of Types for Each Year and for Five Years, Annual Incidence and Percentage of Five Year Total*

Type	Per Cent Each Year					Per Cent 5 Years	Total Cases
	1934	1935	1936	1937	1938		
I	12	10	22	30	21	22	120
II	19	4	10	7	5	7	104
III	13	10	12	13	14	13	190
IV			1	5	6	4	55
V			2	6	6	4	39
VI			1	2	3	2	28
VII			10	18	11	12	172
VIII			3	7	7	5	70
IX			0	4	1	2	36
XIV			1	1	2	1	15
Others *			2	8	17	8	122
Group IV	55	75	39			20	298
Annual incidence number	67	192	301	388	521		1,469
Per cent of 5 year total	5	13	20	26	36	100	

* The term "others" indicates Cooper types X to XIII and XV to XXXII each of which was represented by inadequate numbers of patients to warrant separate presentation (table 16).

The prevalence of pneumococci, especially of the higher types, in the respiratory passages of normal persons introduces a question of the reliability of typing by examination of sputum. The problem is not so much the identification of the pneumococci as it is the relation of the recovered organisms to the pneumonia. The more efficient the method of recovering the organisms, the more probable is the recovery of organisms incidentally present in the nose and throat, methods such as that of mouse passage, used to determine carriers in the normal population, would also find them among patients with pneumonia. Direct examination of the sputum, however, requires large numbers of organisms in the sputum, for otherwise the chances of seeing them are slight. The more crude the method, the more the sputum must be loaded with organisms to give positive results. The more common false negative results become, the more reliable are the positive results likely to be (ruling out laboratory errors). We reviewed the results of the examina-

tion of 249 samples of sputum taken from 157 patients (consecutively admitted to one ward) in whom the presence of pneumonia due to a definite type of pneumococcus was established by the finding of the organisms in several samples of sputum or by culture of body fluids. In only 73 per cent of the samples were pneumococci found. We assume that the remaining 27 per cent of the reactions represent false negative results. Laboratory errors appeared, so far as we could determine, in less than 1 per cent of all examinations. It is probable, then, that the type of pneumococcus recovered from the sputum was the etiologic agent of the pneumonia.

TABLE 2—*Outcome in Cases of Pneumonia, Incidence of Concomitant Conditions, and Outcome and Incidence of Serum Therapy with Such Conditions Present or Absent*

Type	Outcome (%)			Incidence (%) of Concom- itant Condi- tions	Concomitant Conditions (%)					
	Opti- mum*	Death	Compli- cation		Present			Absent		
					Death	Compli- cation	Serum Therapy†	Death	Compli- cation	Serum Therapy†
I	66	17	23	38	23	23	80	14	24	77
II	58	28	26	34	34	20	60	25	29	62
III	58	34	18	57	39	19	24	28	16	12
IV	67	22	15	62	26	3	26	14	33	24
V	61	25	22	59	31	26	74	17	17	57
VI	67	33	11	63	33	17	17	33	0	33
VII	64	24	16	49	28	15	72	20	16	68
VIII	67	20	24	67	28	23	38	4	26	26
IX	69	14	17	67	17	13	0	8	25	17
XIV	69	20	20	47	43	29	29	0	13	17
Others	75	17	11	71	20	7	6	8	19	11
Group IV	65	21	18	47	26	14	0	17	21	0
All types	65	23	19	51	28	17	36	17	21	41

* Survival without complication

† Treatment with type specific serum

Data are presented in tables 2 through 12 concerning the outcome, history, diagnosis, laboratory findings and febrile course of the pneumonias associated with each type. Some of the findings for the four Cooper types represented by 100 or more patients (I, II, III and VII) are outlined in the following paragraphs.

Type I pneumococci were recovered in material from 320 patients, of whom 66 per cent survived without complications (optimum outcome), 23 per cent had complications and 17 per cent died. The total of the three rates is 106 per cent, indicating that 6 per cent of the patients died with complications. Concomitant conditions were recognized in only one third of the patients, many of these disorders being respiratory and very few cardiac. The mortality rate was greater in the presence of known concomitant conditions than in their presumed

absence, as was true of almost every type. Four fifths of all patients with pneumonia due to pneumococci of type I received antipneumococcus serum.²

Of the 75 patients in whom complication developed, 48 per cent had empyema and 20 per cent had pleural effusions,³ while 19 per cent had otitis media. The heart and pericardium were rarely involved (table 3).

The seasonal incidence of type I pneumonia conformed closely to that usually described for more rigorous climates. Nearly one-half the patients were between 20 and 40 years of age, while few were over 60.

TABLE 3—*Relative Frequency (per Cent) of Various Complications Among All Patients with Complications**

Type	Percentage of Patients with Named Complication Among All Those with Complications									
	Empyema	Pleural Effusion	Otitis Media	Menigitis	Pulmonary Abscess	Endocarditis	Pericarditis	Thrombophlebitis	Pericardial Effusion	All Other Complications
I	48	20	19	1	2	2	0	2	1	0
II	34	29	3	9	0	11	9	1	3	0
III	22	35	16	8	3	0	8	0	3	3
IV	33	22	11	11	11	11	0	0	0	0
V	53	6	12	6	6	12	0	0	6	0
VI	0	100	0	0	0	0	0	0	0	0
VII	10	48	10	3	3	3	0	0	7	14
VIII	20	24	20	12	8	0	0	4	0	8
IX	50	33	17	0	0	0	0	0	0	0
XIV	0	67	0	0	33	0	0	0	0	0
Others	31	31	8	8	8	8	0	0	8	0
Group IV	30	31	5	6	5	3	5	8	2	5
All types	33	28	12	5	4	4	3	3	2	1

* Patients with more than one complication are listed once under each.

Almost all were Caucasian or Mexican, and two thirds of the patients were male (table 4).

In about half the histories of patients with pneumonia of type I there was no mention of complaints preceding the onset of pneumonia, while in 43 per cent there were complaints referable to the respiratory tract. The latter rate is probably an understatement of the true incidence. Thirty per cent of the patients were admitted during the first two days following the onset, 60 per cent during the first four days and 81 per cent

2 Evaluation of the effects of such therapy is readily seen to be difficult and to require separate study when it is learned that the treatment itself varied greatly and that there were no controls, serum being given to almost all patients who might be aided by it.

3 Since it is felt that if serial roentgen studies were routinely made, minimal amounts of pleural fluid would be discovered in almost all patients, "pleural effusion" has been termed a "complication" only when it was voluminous enough to attract clinical attention.

during the first six days. In patients without known concomitant conditions, the major symptoms of pneumonia (in the order of frequency) were fever, painful respiration, chill, cough (excluding patients with

TABLE 4—*Distribution (per Cent) of Patients According to Season, Age, Race and Sex**

Type	Season				Age (Yr)				Race				Sex, (% Male)
	May to Sept	Oct and Nov	Dec to Feb	March and April	0 to 19	20 to 39	40 to 59	60 and Over	Cau- cas- ian†	Mexi- can	Negro	Miscel- lane ous‡	
I	22	14	42	23	18	46	29	7	76	18	6	1	67
II	22	13	47	19	19	45	34	5	67	27	7	1	74
III	19	11	54	17	7	29	30	35	74	16	7	2	64
IV	15	21	56	7	13	40	34	13	71	7	20	2	60
V	15	8	55	22	15	44	25	15	73	22	5	0	70
VI	33	21	32	14	8	53	29	11	82	11	7	0	61
VII	15	12	48	24	15	36	36	12	67	23	9	1	68
VIII	17	21	47	15	4	33	37	26	79	11	7	3	61
IX	18	22	45	16	6	47	25	22	75	11	14	0	72
XIV	21	26	27	26	26	20	26	27	80	7	7	7	60
Others	25	16	41	17	12	33	33	23	76	13	10	1	66
Group IV	18	9	47	26	11	49	32	8	70	19	10	1	61
All types	19	13	47	21	13	41	31	15	73	18	8	1	65

* Typing of infants and children was less frequently attempted than that of adults

† Excluding Mexicans

‡ All other races (mostly far Eastern)

TABLE 5—*Analysis of Histories of All Patients Showing Symptoms Preceding Onset of Pneumonia and Number of Days From Onset* to Admission*

Type	Complaints Preceding Onset of Pneumonia, Distribution (%)					Number of Days from Onset to Admission Distribution (%)					
	None Re- corded	Respi- ratory Infec- tion †	Ma- laise ‡	Gastro- intes- tinal	Others						
						1, 2	3, 4	5, 6	7, 8	9 and Over	?
I	48	43	4	2	3	30	30	21	12	6	1
II	46	47	2	1	6	29	34	17	10	8	2
III	39	50	2	1	7	31	26	16	14	9	4
IV	45	35	2	1	15	36	34	16	7	4	2
V	39	49	2	1	12	31	27	28	14	2	0
VI	25	39	7	7	21	43	25	18	11	4	0
VII	50	40	3	2	5	26	30	17	16	10	0
VIII	40	49	0	1	10	30	30	16	12	7	3
IX	31	42	3	0	25	45	20	12	14	11	0
XIV	27	60	0	0	13	33	40	7	0	13	7
Others	32	41	1	4	21	45	22	11	6	15	2
Group IV	43	47	6	1	5	23	33	19	14	7	4
All types	43	45	3	1	8	30	30	18	12	7	2

* "Onset" is understood here as the first appearance of pain on respiration, fever, chill, bloody sputum, dyspnea, prostration or coma, or, in the absence of those symptoms, a sudden change for the worse in an infection of the respiratory tract

† Usually in the upper expiratory tract, with or without complaints referable to other systems

‡ Vague symptoms not referable to any particular system

cough prior to the onset), bloody sputum and dyspnea. At least five of these symptoms were present in 22 per cent of the patients, at least four in 57 per cent and at least three in 82 per cent, while only 4 per cent of the patients had but one symptom. The usual explosiveness of the

syndrome is indicated by the fact that less than one day elapsed between the appearance of the first and the last of these symptoms in 72 per cent of the patients—only 17 per cent, without concomitant conditions, being admitted within one day of the onset (tables 5 and 6)

Definitely atypical pulmonary involvement was rare among patients with type I pneumonias, and nearly one third of the more typically lobal lesions involved more than one lobe Although pneumococci were observed in the blood of 9 per cent of the 90 patients for whom cultures were made, that figure cannot be accepted as indicating the incidence of

TABLE 6—Analysis of Histories of Patients Without Known Concomitant Conditions, Showing Incidence of Major Symptoms of Pneumonia, and Distribution of Patients According to Number of These Symptoms per Patient and to Number of Days Between Onset of First and Last of These Symptoms

Type	Major Symptoms (%)						Distribution (%) of Patients						
							According to No of These Symptoms			According to No of Days Between First and Last Symptom			
	Pain on Respi- ration	Fever	Chill*	Cough†	Bloody Spu tum†	Dysp nea	0 to 2	3 or 4	5 or 6	0 to 1	2 to 3	4 to 6	7 and Over
I	81	85	70	59	40	25	18	60	22	72	16	10	2
II	83	75	61	67	51	22	20	54	26	72	13	9	6
III	82	68	63	76	46	15	24	47	28	79	12	7	1
IV	86	81	67	67	48	33	19	43	38	86	10	0	5
V	75	67	67	42	42	33	37	33	29	67	17	17	0
VI	90	80	90	50	50	20	0	80	20	60	20	10	10
VII	81	67	65	67	52	25	18	56	26	61	19	18	2
VIII	83	91	78	87	35	22	26	43	30	78	22	0	0
IX	75	83	50	58	25	8	25	67	8	75	25	0	0
XIV	100	75	63	63	38	0	25	63	13	75	13	0	10
Others	77	86	63	60	46	34	20	46	34	63	23	6	9
Group IV	82	73	64	63	44	23	19	61	20	76	15	4	6
All types	82	77	66	63	44	23	20	56	24	72	16	8	4

* Rigor or severe chilly sensations
† Only patients whose cough developed at or after the onset of pneumonia are included
‡ Bloody, rusty, brown or orange sputum (the latter terms are often used by Mexicans)

bacteremia, for cultures were made only under special circumstances The maximum total leukocyte count recorded, made during the acute pneumonia, was within normal limits for 11 per cent and between 10,000 and 30,000 for 77 per cent of the patients studied (table 7)

The highest temperature⁴ observed during the first few hours of hospitalization exceeded 103.5 F for 41 per cent of the patients with

4 There are numerous evidences of the progress of the disease, but the only signs that are readily measured are the temperature, the pulse rate and the respiratory rate The respiratory rate is not, according to our experience, measured with sufficient care to be reliable (the nurses usually being too pressed for time) The pulse rate is usually less labile than the temperature, tending to be elevated for some little time after the fever is abolished The temperature has therefore

(Footnote continued on next page)

type I pneumonia but was less than 101.5 F for 13 per cent. There was a generally flat, or horizontal, temperature curve for only one fourth of the patients, while for 63 per cent the temperature curve progressively tended to fall. Fluctuations of the temperature were insignificant for 19 per cent, moderate (usually from 1 to 3 degrees) for 74 per cent and marked for only 4 per cent of the patients. Some further indication of the course is found in the fact that 70 per cent of the patients received oxygen, which is routinely given in the presence, to a moderately alarming degree, of hyperpnea, cyanosis, tachycardia or delirium (table 8).

TABLE 7—*Distribution (per Cent) of Patients According to Pulmonary Involvement, to Incidence of Positive Blood Cultures Among Patients from Whom Cultures Were Taken, and to Maximum Recorded Total Leukocyte Count (in Thousands)*

Type	Pulmonary Involvement								Blood Culture		Maximum Recorded Total Leukocyte Count (in Thousands)†						
	Lobar *				Atypical						No of Patients	Per centage Positive	No of Patients	Total Leukocyte Count			
	No of Lobes				Extent				to 4	to 9				to 19	to 29	Over	
	1	2	3+	Total	Total	Minimal	Mod erate	Exten sive									
	I	64	19	12	95	3	1	1									1
II	54	23	17	94	6	2	1	3	17	29	78	3	14	52	27	5	
III	44	15	7	66	33	10	14	9	26	12	115	2	15	42	26	17	
IV	69	5	7	81	19	2	13	4	11	10	36	3	17	48	28	6	
V	56	19	10	85	15	3	7	5	9	22	38	0	3	66	16	16	
VI	36	18	7	61	40	11	25	4	4	0	17	0	29	47	24	0	
VII	60	18	11	89	11	2	6	3	26	15	107	1	14	50	23	10	
VIII	59	13	10	82	19	9	4	6	16	25	49	2	6	60	22	10	
IX	67	11	3	81	20	3	14	3	6	0	25	0	7	56	23	15	
XIV	53	20	0	73	27	7	13	7	5	40	11	0	0	36	45	18	
Others	46	11	2	59	40	9	24	7	24	4	63	0	25	41	22	11	
Group IV	56	18	10	84	15	5	8	2	13	23	199	1	13	47	30	10	
All types	56	17	10	83	17	5	8	4	242	14	937	1	13	49	26	11	

* "Lobar" includes all involvement not definitely atypical and is chiefly a clinical diagnosis.

† Figures are for the patients for whom leukocyte counts were made during the acute stage of the illness.

In 22 per cent of the cases of type I pneumonia the first normal temperature was observed during the first four days of illness, in 45 per cent between the fifth and the eighth day and in 23 per cent on or after the ninth (only 6 per cent of the patients were admitted on or after the ninth day), there being no defervescence in 11 per cent. Among patients

come to be of great significance, and special attention was devoted to the defervescence and to the recurrence of fever in these patients. Rigid criteria were adopted, the term "normal" indicating a temperature of 99 F or less and "crisis" indicating a fall of temperature during no more than twenty-four hours. The temperature was considered only during the interval in which the course was uncomplicated, hence the statement that in a patient with complication there was "no defervescence" means only that there was none prior to the recognition of the complication.

who died without complication, crisis⁵ was twice as common as lysis, while crisis and lysis occurred with about equal frequency among all other patients. A defervescence was observed in all of the patients who survived without complications and in 96 per cent of those who survived and had complications, but in only 54 per cent of those with complications who died and in 30 per cent of those without complications who died (table 9).

TABLE 8—*Distribution (per Cent) of Patients According to Fever and Incidence of Treatment with Sulfanilamide, Antipneumococcus Serum or Oxygen*

Type	Temperature (F) on Admission					General Appearance of Temperature Chart During Uncomplicated Febrile Course						Incidence (%) of Treatment		
						Trend			Variation †					
	To 100	101	102	103	104 and Over	Plateau	Better	Worse	Insignificant	Moderate	Marked	Sulfanilamide	Serum	Oxygen ‡
I	5	8	18	28	41	25	63	9	19	74	1	9	75	70
II	9	8	17	40	26	35	55	11	14	81	6	11	62	65
III	15	8	26	29	21	34	54	13	12	85	4	17	19	63
IV	7	11	24	33	25	33	56	11	16	78	6	16	25	58
V	8	14	19	32	27	30	51	17	21	69	8	5	66	63
VI	18	14	25	11	32	32	53	14	7	92	0	29	21	54
VII	9	9	23	31	28	25	59	15	16	79	4	14	70	67
VIII	13	16	24	30	17	26	61	13	19	77	4	26	34	54
IX	17	14	28	25	17	22	61	14	14	80	3	33	6	72
XIV	7	13	20	0	60	40	53	7	0	100	0	13	33	67
Others	10	16	29	25	21	29	62	8	7	87	5	20	7	61
Group IV	8	13	26	30	22	30	59	11	16	77	7	0	0	58
All types	9	11	23	29	27	29	59	11	15	80	5	12	39	63

* The distribution according to fever is based on (1) maximum temperature recorded during the first few hours after admission and (2) general appearance of the temperature chart before cure, death or recognition of complications.

† The significance of terms describing trend, or general slope, is as follows: "plateau" means flat, "better," falling, and "worse," rising. Fluctuations designated as "insignificant" were usually less than 1 degree, as "moderate," usually from 1 to 3 degrees, and as "marked," usually more than 3 degrees.

‡ Oxygen was routinely given for dyspnea, cyanosis, tachycardia or delirium.

Of the patients who had a defervescence, a recurrence of fever was noted in 64 per cent of those surviving and having no complications, 80 per cent of the survivors with complications, 76 per cent of those who had complications and died and 70 per cent of those without complications who died (table 10). From these data may be computed the percentage of patients who had a defervescence with no subsequent fever, the results being shown in table 13 for types I, II, III and VII. Type I pneumonia was terminated within the first four days in 15 per cent of

5 "Crisis," as has already been mentioned, was strictly defined as a fall of temperature from peak to less than 99 F in less than twenty-four hours, regardless of the possible cause of the defervescence.

the patients who survived without complications and in 6 per cent of those who died without complications, no complications having been recognized during that time. By the tenth day, however, 71 per cent

TABLE 9—*Distribution (per Cent) of Patients with Respect to Days Between Onset of Pneumonia and First Normal Temperature and to Outcome According to Manner of First Defervescence**

Type	Outcome According to Manner of First Defervescence																			
	Number of Days from Onset to First Normal Temperature †							Not Complicated											Complicated	
								Well					Dead						Well	
	1 or 2	3 or 4	5 or 6	7 or 8	9 or 10	11 and Over	? or No Def- ervescence	Crisis ‡	Lysis §	Crisis	Lysis	No Defervescence	Crisis	Lysis	No Defervescence	Crisis	Lysis	No Defervescence		
I	5	17	24	21	11	12	11	55	45	21	9	70	45	51	4	27	27	46		
II	2	18	22	22	8	13	15	55	45	24	12	64	40	60	0	35	25	42		
III	9	9	20	18	11	14	20	50	50	30	20	50	47	47	6	32	21	47		
IV	7	19	26	16	8	9	16	46	54	20	0	80	33	67	0	50	50	0		
V	3	15	21	24	10	14	14	64	36	40	20	40	38	50	13	20	20	63		
VI	18	18	8	22	11	7	18	56	41	29	14	57	0	100	0	0	50	50		
VII	3	14	23	20	18	11	12	54	46	37	11	52	43	57	0	33	17	50		
VIII	13	17	10	21	11	14	13	57	40	0	50	50	44	56	0	25	25	50		
IX	6	14	17	25	14	14	11	52	48	20	40	40	33	33	33					
XIV	7	7	33	13	0	27	13	56	44	33	0	67	67	33	0					
Others	9	17	22	17	6	16	11	51	49	24	18	59	33	56	11	25	25	50		
Group IV	5	7	19	21	12	21	16	39	60	22	20	59	32	63	0	33	17	50		
All types	6	13	21	20	11	15	14	51	49	26	16	58	40	56	4	29	24	47		

* All data concerning the temperature refer exclusively to the interval in which no complication had appeared

† By "normal" is meant 99.0 F or less

‡ Less than twenty-four hours from peak to first normal temperature

§ More than twenty-four hours from peak to first normal temperature

TABLE 10—*Incidence of Recurrence of Fever † in Patients Who Had a Defervescence (Tabulated According to Outcome)*

Type	Not Complicated		Complicated	
	Well	Dead	Well	Dead
I	64	70	80	76
II	72	100	75	86
III	76	87	86	90
IV	81	100	83	100
V	67	100	43	100
VI	89	100	100	0
VII	67	94	76	100
VIII	60	67	78	100
IX	60	100	100	
XIV	78	100	67	
Others	73	86	63	100
Group IV	60	100	66	83
All types	68	93	75	87

* "Fever" means a temperature of 99.0 F or over, and only the temperature during the uncomplicated interval is considered

of the patients surviving without complications were cured, 60 per cent of those having no complications and dying had died and 43 per cent of the complications had been recognized (table 11)

The duration of hospitalization for type I pneumonia and its sequelae was less than two weeks in the case of 67 per cent of patients who survived and had no complications and in 17 per cent of those with complications who survived. Of the patients who died and had no com-

TABLE 11—*Distribution (per Cent) of Patients by Outcome According to Duration of Uncomplicated Febrile State**

Type	Not Complicated												Complicated					
	Well						Dead						Well or Dead					
	1 to 4	5 to 7	8 to 10	11 to 14	15 and Over	?	1 to 4	5 to 7	8 to 10	11 to 14	15 and Over	?	1 to 4	5 to 7	8 to 10	11 to 14	15 and Over	?
I	15	28	28	17	12	0	6	36	18	18	12	9	0	11	32	23	31	3
II	8	32	25	20	13	2	0	24	24	18	35	0	11	15	23	21	26	4
III	10	26	24	24	15	2	4	39	31	18	7	2	3	12	33	21	26	6
IV	11	35	27	8	19	0	20	60	10	0	0	10	0	38	0	26	37	0
V	19	31	25	11	14	0	0	30	20	20	30	0	8	24	31	8	31	0
VI	11	28	39	6	17	0	0	57	14	14	14	0	0	33	33	33	0	0
VII	13	25	28	19	14	0	6	23	46	18	9	0	0	11	37	26	26	0
VIII	17	23	33	12	13	2	17	17	67	0	0	0	0	6	24	24	41	6
IX	8	12	40	8	32	0	0	60	0	20	20	0	0	17	50	0	33	0
XIV	0	33	22	22	22	0	0	33	0	0	33	33	0	33	33	0	33	0
Others	17	30	29	6	17	1	29	30	6	6	18	12	8	8	16	8	62	0
Group IV	5	26	27	22	18	3	14	28	26	8	16	10	4	10	14	21	42	11
All types	12	27	28	17	15	1	9	33	26	13	14	5	3	12	25	24	34	2

* The duration of the uncomplicated febrile state is the number of days from onset to the last febrile temperature (over 99 F) before cure, death or recognition of complications, and includes any intervening afebrile intervals.

TABLE 12—*Distribution (per Cent) of Patients by Outcome According to Number of Days Hospitalized for Pneumonia or Its Sequelae*

Type	Not Complicated										Complicated							
	Well					Dead					Well				Dead			
	1 to 6	7 to 10	11 to 14	15 and Over	1	2	3	4 or 5	6 to 8	9 to 14	15 and Over	1 to 10	11 to 14	15 and Over	1 or 2	3 to 7	8 to 14	15 and Over
I	5	37	26	32	18	24	12	27	12	3	3	8	9	83	27	27	23	23
II	6	23	27	43	18	12	12	30	18	12	0	20	7	73	8	32	16	42
III	10	19	25	46	20	15	20	13	22	10	0	0	27	73	42	26	27	5
IV	3	27	32	38	30	30	10	10	10	10	0	0	33	67	0	50	0	50
V	3	34	33	31	10	20	10	10	20	20	10	13	0	87	40	20	20	20
VI	11	34	28	28	0	0	43	29	14	14	0	0	0	100	50	50	0	0
VII	6	28	28	37	20	14	17	26	12	9	3	20	33	48	34	17	50	0
VIII	4	41	26	30	0	17	50	0	34	0	0	11	11	78	13	25	13	50
IX	4	28	20	48	0	0	0	80	0	20	0	0	33	67				
XIV	0	22	22	56	0	33	67	0	0	0	0	33	33	33				
Others	8	28	20	44	12	29	18	24	0	12	6	0	22	78	0	25	25	50
Group IV	10	34	23	35	8	14	33	28	10	4	4	9	10	81	33	17	33	17
All types	7	31	25	37	15	17	21	23	13	8	3	10	16	75	27	25	24	23

plications about 80 per cent died within the first five days of hospitalization and 18 per cent within the first day. Of those with complications who died, 54 per cent died within the first week and 27 per cent within the first two days of hospitalization (table 12).

Type II pneumococci were recovered in material taken from a total of 104 patients during the five year period, and this was the fifth most

frequent type during 1937-1938. Type II pneumonia carried a suggestively higher mortality rate than did type I, but there was no difference in their complication rates. Concomitant conditions, present in one third of the patients, were accompanied by an elevation in the death rate as compared with that for patients in whom they were not recognized. About two thirds of all complications involved the pleura, as was true with type I, but otitis media was rarely observed. The heart and pericardium, however, were more frequently involved than in disease due to any other type.

Compared with patients having pneumonia of type I, a suggestively greater proportion of those with type II were Mexican and the incidence of males was slightly increased. There was no observed difference between the two types in the distribution according to age or season or in the complaints preceding the onset of pneumonia. For type II, the major symptoms of pneumonia were more frequently cough and

TABLE 13—*Incidence (per Cent) of Patients Who Had a Defervescence with No Subsequent Recurrence of Fever Before Cure, Death or Recognition of Complications (Tabulated According to Outcome)*

Type	Not Complicated		Complicated	
	Well	Dead	Well	Dead
I	36	9	19	13
II	28	0	25	8
III	24	6	13	5
VII	33	3	24	0

bloody sputum and less often fever and chill. Few of the pulmonary lesions were distinctly atypical (only 6 per cent), but 23 per cent of the more typically lobar lesions involved two lobes and 18 per cent three or more lobes—a more extensive pulmonary involvement than that found in pneumonia of any other type. This evidence of the invasive powers of type II pneumococci was confirmed by an observed increase of 20 per cent⁶ in the incidence of bacteremia as compared with that associated with type I.

Compared with the temperature of patients with type I pneumonia, that of patients with type II was lower, exceeding 103.5 F in a significantly smaller proportion, while the febrile course tended more often to be horizontal and the fluctuations to be somewhat greater. There was less often a recurrence of fever following the defervescence (except in patients with complications who survived). The febrile course was longer in patients without complications, and complications developed

6 No statistical significance may be attached to that difference, however, because of the small number of patients studied and the special circumstances under which the cultures were usually taken.

earlier in the disease. The period of hospitalization was greater for type II than for type I, in the case of all patients except those surviving and having no complications.

Type III pneumonia was the third most common type during 1937 and 1938. During the five year period there were 190 patients, of whom 58 per cent survived without complication (the optimum outcome rate being lower for types II and III than for any other type), 34 per cent died (the mortality for types III and VI exceeding that for any other type) and 18 per cent had complications (10 per cent dying with complication). Concomitant conditions were recognized in over half the patients. Of the complications observed, only 57 per cent were pleural (22 per cent empyema and 35 per cent pleural effusion). It is interesting to examine the relation between the gross incidence of all pleural involvement and the frequency with which such involvement was found to be infected (empyema), as shown in table 14 for types I, II, III

TABLE 14—*Incidence (per Cent) of Pleural Involvement Among All Complications and of Empyemas Among Pleural Involvements*

Type	Pleural Among All Complications, per Cent	Empyemas Among Pleural Complications, per Cent
I	68	71
II	63	54
III	37	39
VII	58	17

and VII. These data suggest but by no means prove that the less often the pleura is clinically involved, the less often is such involvement likely to be an empyema.

The usual seasonal trend was exaggerated for pneumonia of type III. The age distribution was higher than for any other type, 65 per cent of the patients being over 40 years of age and 35 per cent over 60. A suggestively smaller proportion of the patients were asymptomatic prior to the onset, while the unfolding of symptoms following the onset was even more rapid than in type I or II. Atypical lesions were much more frequent than in type I or II, but the more typically lobar lesions were no less extensive than for type I. Bacteremia was found to occur in 12 per cent of the 26 patients in whose cases cultures were made. The temperature at the time of admission was definitely lower than in types I and II, the general appearance of the chart being similar to that of type II. It is interesting to note that patients surviving without complication ran a longer febrile course, while among those dying and having no complications death tended to occur earlier in patients with type III pneumonia than in those with type I or II. Complications developed at about the same time following the onset as in patients with type I.

Type VII pneumonia was second in frequency during 1937 and 1938 and was represented by 172 patients. Half of these had concomitant conditions, and 70 per cent received serum therapy. In 16 per cent complications developed, 24 per cent died with complications. Excluding types VI and XIV, more of the complications associated with type VII pneumonia were pleural effusion and fewer were empyemas than those accompanying any other type, the total of pleural involvements being the same, however, as with type III.

The curve of age incidence was symmetric for type VII pneumonia. Complaints preceding the onset were similar to those associated with type I, while of the major symptoms, chill and fever occurred with the same frequency as in type III, cough and bloody sputum as in type II. The concurrence of symptoms paralleled that for types I and II, but the symptomatic maximum was not reached so rapidly. The lesion was distinctly atypical in 11 per cent of the patients, while a third of the more typical lesions extended over more than one lobe. Bacteremia was demonstrated in 15 per cent of the 26 patients studied. On the average the leukocyte count was about the same as for type I and the temperature on admission as for type II, while the general febrile course lay between those for types I, II and III. Among half of the patients who died without complications, death occurred between the eighth and the tenth day of illness. Over half of the patients with complications who survived required hospitalization for less than two weeks (reflecting the high incidence of simple pleural effusions), while among all the patients who had complications and died, death occurred within two weeks of admission.

It is rather natural to assume that types which frequently produce atypical lesions are likely to be less "virulent" than those which usually cause typically lobar pneumonia. Such a view is untenable, however, on the basis of the data presented in table 15, in which it is seen that the incidence of atypical lesions is apparently not related to their mortality rate, to the extent of lobar lesions or to the mortality rate for lobar lesions in one lobe.

The remaining types are of profound interest to students of pneumonia. In this series, however, the numbers of patients are too small to warrant a textual outline of the findings. The data concerning types IV, V, VI, VIII, IX and XIV are included in tables 2 through 12 for the benefit of those especially concerned with pneumonia. The types which are pooled as "others" are enumerated in table 16.

Data concerning the complications of pneumonia are presented in table 17. Of all complications, 61 per cent involved the pleura (33 per cent being empyema), 12 per cent the middle ear, 8 per cent the heart and pericardium, 7 per cent the endovascular system and 5 per cent the

TABLE 15—*Cooper Types in Order of Frequency with Which They Produced Atypical Lesions, Percentage of Atypical Lesions Among All Lesions and of One Lobe Lesions Among All Lobar Lesions, and Mortality Rates for One Lobe and for Atypical Pneumonia**

Type	Per Cent Atypical Among All	1 Lobe per Cent Among Lobar	Mortality per Cent	
			Atypical	1 Lobe Lobar
I	3	66	27	8
II	6	57	50	14
VII	11	67	42	13
V	15	66	33	15
IV	19	85	20	21
VIII	19	73	8	15
IX	20	84	14	8
XIV	27	73	75	0
III	33	67	38	20
VI	40	60	36	10
Others	40	77	20	9

* The group for each type except III and "others" included less than 20 patients with atypical pneumonia, there were more than 20 with one lobe lobar pneumonia in the group with each type except VI and XIV. Actual numbers may be computed from tables 1 through 12.

TABLE 16—*Enumeration of "Other" Types, Showing Total Number of Patients, Number Dead and Number with Complications*

Type	Total Number of Patients	Number Dead	Number with Complica- tions
X	3	1	0
XI	11	2	2
XII	14	1	1
XIII	2	0	0
XV	13	5	1
XVI	7	1	1
XVII	12	3	1
XVIII	10	0	0
XIX	10	2	2
XX	7	2	1
XXI	2	0	0
XXII	4	0	1
XXIII	9	1	1
XXIV	2	0	1
XXV	7	1	0
XXVII	1	0	0
XXVIII	2	2	1
XXIX	5	0	0
XXXII	1	0	0
Total	122	21	13

meninges. Except among patients with otitis media or thrombophlebitis, the mortality was higher in the presence than in the absence of complications. Although in only 19 per cent of all (1,469) patients did complications develop, 33 per cent of those in whom they occurred had more than one complication. The distribution of patients with complications according to age, sex and leukocyte count did not differ remarka-

bly from that of patients without complications. Among patients with complications, the blood cultures were more frequently positive, concomitant conditions were slightly less common and serum was somewhat more often administered.

During recent years there has been an increasing tendency to classify pneumococcic pneumonia etiologically. One may question whether this trend owes more to a realization of fundamental differences between the types than to use of type-specific serum. The practical importance of classification according to types is minimized by the fact that there is such a large number of them that it is impossible to bear in mind the

TABLE 17—*Complications of Pneumonia**

Complication	Incidence per Cent Among All Complications	Deaths, per Cent	Distribution (%) of Patients									
			According to Type of Organism †							According to Pulmonary Lesion		
										Lobar		Atypical
			I	II	III	IV	V	VII	VIII	1 Lobe	2+ Lobes	
Empyema	33	34	40	11	7	3	8		5	47	43	9
Pleural effusion	28	26	19	11	14	2	1	15	6	60	36	4
Otitis media	12	10	4	3	2	5	5	8	15	68	18	16
Meningitis	5	100	6	17	17	6	6	6	17	32	39	28
Pulmonary abscess	4	69	15	0	8	8	8	8	15	35	54	8
Acute endocarditis	4	100	15	31	0	8	15	8	0	38	54	8
" "	3	78	0	33	0	33	0	0	0	22	67	11
" "	3	0	21	11	0	0	0	0	11	33	67	0
" "	2	75	13	13	13	0	13	25	0	50	50	0
" "	1	67	0	33	0	0	0	0	33	33	67	0
" "	4	50	20	0	7	0	0	29	14	50	36	14
Complications ‡		53	27	10	12	3	5	10	6	52	37	10
No known complication		20	21	6	13	4	4	12	4	57	25	19

* Patients with more than one complication are listed once under each.

† Each patient is listed here once only.

‡ Only the more common Cooper types are listed, the unlisted types (VI, IX to XXIII and group IV) bring the total to 100 per cent.

§ Listed with the number of cases and, in parenthesis, the number of deaths, the "other complications" were: mediastinitis 2 (2), mastoiditis 2 (1), parotitis 2 (1), arthritis 1 (1), massive pulmonary fibrosis 1 (0), and suppurative lymphadenitis 1 (0).

characteristics of each. One may also inquire whether other factors, such as the character of the lesion or the presence of concomitant conditions may not be of greater prognostic importance than the type of organism.

In tables 18, 19, 20 and 21 are presented the incidence and outcome for the variables which were used to characterize pneumonias associated with the various types of organism, along with the distribution of the types and the incidence of concomitant conditions and of serum treatment. Certain of the findings are summarized in the following paragraphs.

A peak in the age incidence was observed in the figures for the decade 30 to 39, while almost 60 per cent of the patients were between

20 and 50 years of age. With the exclusion of the first decade,⁷ the mortality rate rose and the optimum outcome rate declined with increasing age, while the complication rate remained relatively constant (a peak may be suspected in the forties). The proportion of cases of pneumonia due to organisms of types I and II fell off with advancing age, while infection with types III and VIII increased in frequency. The incidence of concomitant conditions increased with age, but the same changes in incidence and outcome were noted for patients without known concomitant conditions as for all patients. Although the frequency of serum treatment declined with increasing age, the change may be ascribed entirely to the changing type distributions (table 18).

Three fourths of the patients were Caucasian, and a fifth were Mexican.⁸ Concomitant conditions were less commonly recorded among the latter (perhaps because of limitations in the histories due to difficulty with language), and there was a definite increase in the incidence of pneumonia of types II and VII. The complication rate was suggestively lower and the optimum outcome rate higher among Mexicans than among Caucasians, but the mortality rates were equal. Only 8 per cent of the patients were Negroes, and among them type I was less commonly the causative organism. There was a significant increase in the mortality rate of Negroes over that of Caucasians, but the complication and optimum outcome rates were not altered. Fifteen patients were of other races, largely far Eastern. The difference between the outcome among them and that among other races carries little statistical weight (table 18).

Sixty-five per cent of the patients were men. Their mortality rate definitely exceeded that of the women, a difference that cannot be explained on the basis of type distribution, incidence of serum treatment or concomitant conditions (table 18).

In 43 per cent of the patients the history either made no mention of complaints preceding the onset of pneumonia or definitely stated that they were absent, while in 48 per cent there were complaints indicating that some infection of the respiratory tract preceded the onset. The latter group had a suggestively lower mortality rate. Associated conditions were present in most patients with prodromal symptoms referable to a system other than the respiratory or the gastrointestinal, the mortality rate being somewhat elevated and the rarer types more common than usual (table 19).

7 One may not accept at face value either the incidence or the outcome for infants and children, since typing was attempted in their cases only when the children were exceptionally ill or had complications which made the recovery of organisms relatively easy.

8 Of the entire hospital population about 20 per cent are usually Mexican and 7 per cent Negro.

TABLE 18—Outcome Attending Variations in Month, Age, Race and Sex

Month	Variable	Total No of Patients	Incidence (%)	Outcome (%)		Distribution (%) by Type †										Concomitant Conditions (%)	Serum Therapy (%)
				Optimum ‡	Death	1	2	3	4	5	6	7	8	9	10		
January		241	16	65	21	17	9	16	11	7	12	14	1	1	20	50	36
February		228	16	61	25	20	7	11	12	3	6	12	1	1	21	44	29
March		161	11	65	20	23	19	7	12	1	1	10	1	?	32	43	35
April		143	10	68	22	16	30	5	7	3	6	12	1	5	19	47	41
May		65	4	71	17	17	29	6	12	1	9	12	3	15	23	57	42
June		69	5	59	25	26	26	1	1	19	5	11	5	12	16	51	41
July		57	4	65	23	23	26	1	9	12	8	11	5	12	20	49	47
August		43	3	70	14	16	26	1	1	21	9	11	5	12	16	41	41
September		50	3	72	18	16	12	1	1	8	13	8	8	9	23	10	17
October		80	5	63	25	21	22	1	10	5	10	3	6	6	10	66	40
November		113	8	61	29	17	23	8	11	2	13	8	8	8	18	58	40
December		219	15	66	24	15	22	5	10	3	15	13	3	9	28	66	40
0 to 9		26	2	27	15	51	30	6	15	6	15	1	1	9	30	57	45
10 to 19		163	11	77	9	17	11	4	4	8	4	11	0	16	17	56	16
20 to 29		282	19	76	8	18	28	11	11	7	5	11	2	15	18	38	19
30 to 39		324	22	66	20	19	27	9	9	8	4	10	3	12	18	31	15
40 to 49		261	18	62	21	21	23	6	10	1	5	10	1	13	26	43	48
50 to 59		199	14	56	38	18	21	8	9	16	1	11	8	10	19	61	10
60 and over		214	15	54	40	14	18	7	16	31	1	11	5	11	22	72	28
Caucasian		1,071	73	64	21	20	10	6	13	13	1	11	19	23	11	34	34
Mexican		261	18	69	20	15	22	11	12	11	5	15	19	12	20	53	10
Negro		122	8	60	29	20	15	6	11	27	0	1	12	1	21	39	40
Others		15	1	10	33	33	7	7	27	0	7	13	20	26	24	54	28
Male		961	65	63	25	19	22	8	13	1	1	12	17	3	20	53	10
Female		508	55	68	18	19	21	5	14	1	11	3	17	5	19	18	11

* In the first decade typing was attempted only under special circumstances
† In this and the other tables "optimum" means survival without complication
‡ Arabic numerals indicate Cooper types

TABLE 19—*Analysis of Histories with Respect to Complaints Before Onset, to Days Between Onset and Admission and to Nature, and Duration of Symptoms*

	Complaints prior to onset †	Variable	Total No of Patients	Incidence (%)	Outcome (%)		Distribution (%) by Type								Concomitant Conditions (%)	Serum Therapy (%)	
					Optimum	Death	1	2	3	5	7	8	Other Cooper Types IV				
		None	626	43	64	24	18	25	8	12	4	14	4	14	20	45	40
		Infection of the upper respiratory tract	655	15	68	19	20	21	7	15	4	11	16	21	48	39	
		Malaria	49	1	59	20	25	29	4	8	2	10	0	12	35	43	45
		Gastrointestinal	22	1	64	18	18	23	5	9	0	14	5	37	9	68	50
		Others	117	8	55	37	17	8	5	12	6	8	6	44	12	91	29
Number of days from onset to admission	1		265	18	70	17	18	20	6	14	5	9	6	28	13	62	42
	2		182	12	75	17	12	24	8	13	2	11	3	19	19	48	46
	3		231	16	64	20	22	26	8	8	4	10	6	15	22	49	39
	4		205	14	66	24	15	18	8	15	3	15	3	15	22	41	38
	5		176	12	69	18	16	27	5	14	5	11	4	14	21	40	40
	6		84	6	58	27	23	21	11	8	10	13	6	7	23	46	44
	7		153	10	56	31	27	19	7	15	5	15	5	11	24	52	35
	8		26	3	73	12	19	38	0	12	4	15	1	8	19	38	46
	9		10	1	50	30	30	40	10	10	0	10	0	10	20	50	50
	10		25	2	44	36	24	20	12	12	0	20	0	12	16	64	24
	11 and more		80	5	58	33	23	13	5	14	1	13	6	30	20	60	21
	?		32	2	28	59	34	12	6	22	0	0	6	12	11	53	16
Major symptoms of pneumonia ‡ A Symptoms	Pain on respiration		591	82	68	17	19	27	10	11	3	12	3	13	22	42	
	Fever		554	77	69	15	20	30	9	10	3	10	4	12	21	43	
	Chill		478	66	72	15	17	29	9	11	2	12	4	12	21	45	
	Cough		456	64	68	17	18	26	10	12	2	13	1	12	22	41	
	Bloody sputum		319	44	66	19	19	24	11	12	3	14	3	12	22	44	
	Dyspnea		169	23	58	20	30	30	9	7	5	12	3	13	21	42	
	None		15	2	27	10	60	13	7	13	13	0	13	0	40	27	
	1		31	4	35	19	29	26	10	23	6	13	0	12	10	26	36
	2		98	11	71	13	17	26	10	11	5	11	1	12	20	36	
	3		187	26	61	21	26	26	9	11	1	12	2	11	25	40	
	4		216	30	73	13	19	32	9	9	3	12	3	9	24	46	
	5 or 6		177	24	67	19	16	25	10	13	1	12	1	15	18	43	
	C Number of days between onset of first and last symptom	0 or 1		524	72	66	19	21	27	10	12	3	10	3	11	33	39
2 or 3			114	16	78	7	16	27	8	9	1	14	4	15	20	17	
4 to 6			60	8	55	18	30	33	10	10	7	25	0	5	10	50	
7 and over			26	4	58	31	23	15	15	1	0	8	0	24	35	35	

* Onset is defined as first appearance of chill, fever, pain on respiration, bloody sputum, dyspnea, prostration or coma, or, in their absence, of sudden change for the worse during an infection of the respiratory tract
 † Complaints preceding the onset are studied for all patients
 ‡ Only patients without known concomitant conditions were studied The terms "chill," "cough" and "bloody sputum" are explained in the footnote to table 6

The major symptoms of pneumonia were studied only in the histories of patients without known concomitant conditions. Cough being disregarded if it was present before the onset of pneumonia, the symptoms in the order of frequency were pain on respiration, fever, chill, cough, bloody sputum and dyspnea. In patients who complained of dyspnea complications developed more often, a difference which carries considerable statistical weight and cannot be ascribed to the type distribution. Five or all six of these symptoms were present in 24 per cent of the patients, at least four in 54 per cent and at least three in 80 per cent. Three fourths of the patients reached their symptomatic maximum within the first day of the disease, but in them the outcome was considerably worse than in patients whose symptoms developed over a period of two or three days (table 19).

Thirty per cent of the patients were admitted within two days of the onset of pneumonia, 60 per cent within four days and 76 per cent within seven days, the average interval being four and seven-tenths days (table 19). The mortality and complication rates rose with increasing delay in admission, but since many of the patients received serum, the effectiveness of which declines with delay in administration, it became important to study the outcome in patients who did not receive serum (these are not controls for the treated group, however). The results of that observation are given in table 22. It is apparent that the day of admission is considerably less important when serum treatment is not given than when it is given.

The pulmonary involvement was rather typically lobar in 84 per cent of all patients. Of the lesions in this group, 68 per cent were confined to one lobe and 20 per cent to two lobes, while 12 per cent extended over three or more lobes. Only 17 per cent of the patients had lesions that were distinctly atypical clinically or found to be atypical at autopsy when they had been suspected ante mortem of being so. Of these, 29 per cent were minimal (that is, confined to a small area, usually at the base of one lung), 47 per cent moderate (usually involving the bases of both lungs or a considerable single area) and 24 per cent extensive (usually involving a large proportion of the lung). Concomitant conditions were more common in association with atypical than with lobar lesions regardless of their extent, they were also found to be increasingly common with increasing extent of the lesion, regardless of its character. The incidence of pneumonia of types I, II and VII was considerably greater in patients who had lobar than in those who had atypical lesions, while the incidence of type III pneumonia and of the rarer types was greater in patients who had atypical lesions. Serum was much more often administered when the involvement was lobar. The outcomes are of great interest. Arranged with respect to outcome, from best to worst,

the lesions were minimal atypical, one lobe lobar, moderate atypical, two lobe lobar, extensive atypical, and lobar lesions of three or more lobes (table 20)

Blood cultures were usually taken under special circumstances, and one may not accept either the incidence or the outcome as representative. One may accept the difference in outcome between patients with demonstrated bacteremia and those with negative cultures, however, the difference being similar to that usually reported (table 20)

The average total leukocyte count, made during the acute pneumonia, was slightly under 19,000, half of the counts being between 10,000 and 20,000. Patients with counts under 5,000 had extremely poor outcomes, which would be consistent with destruction of the cells at a rate exceeding their production. No difference in outcome, type distribution or incidence of concomitant conditions was found between that group of patients and those with counts over 5,000 (table 20)

The temperature at the time of admission exceeded 103.5 F in 27 per cent of the patients, 102.5 F in 56 per cent and 101.5 F in 79 per cent. The incidence of concomitant conditions and of type III pneumonia fell off with increasing degrees of fever, while types I and II tended to become relatively more common. The mortality rate diminished with increasing fever, the complication rate showing, if anything, a slight tendency to rise. These same alterations in outcome in relation to temperature on admission were found in patients without known concomitant conditions (table 21)

Almost three fourths of the patients had a febrile course⁹ that could be described as "in general either horizontal or falling, with moderate fluctuations." The general trend, or slope, of the temperature curve was downward (better) for 60 per cent of the patients, horizontal for 29 per cent and upward (worse) for 11 per cent. The fluctuations were moderate for 81 per cent, insignificant for 15 per cent and marked for only 4 per cent. Regardless of the extent of the fluctuations the outcome was best when the trend was downward and worst when it was upward, and regardless of the general trend the outcome was probably best when the variations were minimal and worst when they were marked (table 21)

The average time from the onset to the first normal temperature was seven and six-tenths days with 41 per cent of the patients becoming afebrile for the first time between the fifth and the eighth day. The outcome tended to become worse with increasing duration of continuous fever. Almost half the patients died who had no defervescence⁹ (table 21)

⁹ All aspects of the temperature are considered only for the interval before the recognition of complications, if any

TABLE 20—*Analysis of Diagnosis, Blood Culture and Leukocyte Count*

Pulmonary involvement	Variable	Total No of Patients	Incidence (%)	Outcome (%)		Distribution (%) by Type							Concomitant Condi- tions (%)	Serum Therapy (%)
				Opti- mum	Death	1	2	3	5	7	8	Other Cooper Types	Group IV	
Lobar (No of lobes)	1	823	57	73	13	18	25	7	10	1	13	5	21	13
	2	237	17	56	27	22	27	9	11	1	12	1	21	11
	3 and over	140	10	28	61	34	26	13	10	1	14	5	21	14
Atypical	Minimal	69	5	91	7	3	4	3	28	3	6	9	23	12
	Moderate	124	8	61	26	10	3	1	21	3	8	2	20	19
	Extensive	56	1	36	39	27	7	5	32	5	9	7	11	23
Blood culture	Positive *	33	14	24	67	45	24	13	9	6	12	12	9	58
	Negative †	209	86	66	22	23	37	6	11	3	11	6	5	65
	Cultures	242	16	60	28	26	35	7	11	4	11	6	5	64
Maximum recorded total leukocyte count (in thou- sands)‡	No cultures	1,227	84	66	22	18	19	7	13	4	12	1	23	34
	1 to 4	12	1	25	75	8	17	17	17	0	17	8	17	25
	5 to 9	123	14	68	21	14	18	9	14	1	12	2	20	40
	10 to 14	227	24	64	20	22	21	9	11	5	12	6	18	17
	15 to 19	230	24	70	17	20	22	9	10	6	11	7	22	38
	20 to 24	154	16	65	19	20	21	9	12	1	10	5	23	38
	25 to 29	89	9	63	19	21	20	8	11	2	10	1	26	39
	30 and over	101	11	66	20	24	21	4	18	6	11	5	19	46

* One or more cultures positive

† All cultures negative

‡ The figures are for 99 patients during acute illness

TABLE 21.—Analysis of Temperature Pattern to Recognition of Complications, of the Duration of Hospitalization and of the Treatment

	Variable	Total No of Patients	Incidence (%)	Outcome (%)			Distribution (%) by Type						Concomitant Conditions (%)	Serum Therapy (%)
				Optimum	Death	Complication	1	2	3	5	7	8	Other Cooper Types IV	
Temperature on admission	Trend													
	Insignificant fluctuations													
	Moderate fluctuations													
	Marked fluctuations													
	Number of days from onset to first normal temperature													
Manner of defervescence	Yes													
	No													
	Yes													
	No													
	Yes													
Recurrence of fever	Yes													
	No													
	Yes													
	No													
	Yes													
Manner of defervescence	Yes													
	No													
	Yes													
	No													
	Yes													
Recurrence of fever	Yes													
	No													
	Yes													
	No													
	Yes													

Number of days from onset to last febrile temperature	1 to 4	140	10	79	17	6	21	6	10	6	9	6	22	14	51	52
	5	107	7	61	28	15	19	11	15	4	11	4	23	14	50	41
Number of days in hospital for pneumonia or its sequelae	6	120	8	73	21	8	23	23	9	4	11	4	21	23	45	44
	7	149	10	73	25	7	23	23	15	5	9	3	19	19	51	38
	8	146	10	66	26	15	22	22	12	2	13	5	20	22	49	36
	9	133	9	63	23	21	29	29	11	6	15	5	13	15	49	50
	10	119	8	70	17	19	17	17	14	3	15	8	18	16	44	34
	11	83	6	70	22	13	27	27	13	2	12	2	9	25	58	33
	12	69	5	62	14	26	17	17	10	6	19	6	9	20	52	38
	13 or 14	96	6	61	16	29	24	24	24	1	13	4	5	22	47	28
	15 and over	275	18	51	23	34	19	8	10	4	9	5	20	24	53	37
	1	48	3	0	100	27	19	8	29	2	17	2	10	12	60	37
	2	53	4	0	100	23	21	4	19	8	11	2	19	17	61	34
	3	60	4	5	95	10	10	3	20	2	10	7	15	33	63	25
	4	41	3	29	71	15	12	10	17	0	22	0	27	17	49	32
	5	54	4	24	74	17	22	11	17	4	4	2	19	26	50	24
	6	51	3	63	29	6	16	6	18	6	16	1	12	25	41	49
	7	82	6	79	17	7	23	6	7	4	11	7	17	22	44	39
	8	97	7	86	12	7	36	6	7	5	10	8	9	17	47	53
	9	79	5	78	15	13	27	8	15	6	11	4	14	16	40	43
	10	98	7	86	9	9	15	5	8	2	13	6	24	26	47	36
	11 to 14	285	19	83	6	13	22	7	12	5	14	5	17	18	49	38
	15 to 21	262	18	85	5	13	21	10	11	3	12	3	20	19	49	40
	22 and over	261	18	51	5	48	23	6	13	4	8	7	16	21	55	39
Treatment	Oxygen															
	Yes	932	63	54	32	22	24	7	13	4	12	4	17	18	51	44
Sulfanilamide	Yes	87	6	76	10	16	3	1	24	2	5	11	53	0	64	0
	No	482	33	66	20	21	46	11	5	7	21	4	7	0	47	100
Serum	Yes	87	6	69	18	22	30	11	14	3	24	7	11	0	51	100
	No	813	55	62	21	18	8	5	16	2	6	4	21	37	51	0
Yes/no	Yes	174	12	72	14	19	17	6	19	3	14	9	32	0	57	50
	No	1,295	88	61	24	19	22	7	12	4	11	4	17	23	50	37
Yes/no	Yes	569	39	66	19	21	14	11	6	7	21	4	6	0	47	100
	No	900	61	64	25	17	8	4	17	2	6	5	25	33	53	0

* The significance of the terms used in the table is as follows: "normal" means a temperature of 99 F or less, "fever," over 99 F. The temperature on admission is the maximum during the first few hours in the hospital. The febrile course was determined by the appearance of the chart among the terms describing trend, or general slope, is "plateau" meaning horizontal, "better," falling and "worse," rising. Fluctuations, or variations termed "insignificant" were usually of less than 1 degree, "moderate," usually from 1 to 3 degrees, and "marked," usually over 3 degrees. "Crisis" signifies fall from peak to normal during twenty-four hours or less. "No defervescence" means none prior to cure death or complication. 3 patients left the hospital apparently almost cured though still febrile, and were listed as having "optimum" outcome. Recurrence of fever was studied only for patients who had a defervescence.

Crisis and lysis occurred with nearly equal frequency, the mortality rate being slightly lower in patients with lysis and the complication rate slightly lower in those with crisis. There were 562 patients not treated with serum who survived without complication, and a further analysis was conducted on them. It was found that the incidence of crisis fell off as the time from the onset to the first defervescence increased (from 65 per cent for patients with early defervescence to about 30 per cent for those with late defervescence), while the incidence of recurrence of fever remained virtually constant for various intervals from the onset to the first normal temperature. There was a recurrence of fever in 74 per cent of the patients who had a crisis and in 62 per cent of those who had a lysis. The first defervescence had been by crisis in 48 per cent of patients who had a recurrence of fever and in 35 per cent of those who did not have a recurrence. Among all patients who received no serum, in those with crisis the mortality rate was 16 per cent while in those with lysis it was 10 per cent. Some of the foregoing findings may be generalized as follows. The longer the patient is continuously febrile, the less likely is the defervescence to be by crisis, early defervescence is not more likely to be followed by a recurrence of fever than is late, a crisis is more likely to be followed by a recurrence than is a lysis, crisis carries less assurance that the patient will survive than does lysis, but slightly more assurance that he will avoid complications. In table 2 it is seen that there was a defervescence (before recognition of the complications) in almost all patients who had complications but survived and in only half of those who died with complications. It is probable, then, that the development of complications before the temperature has fallen below 99.0 F is much more serious than if the complication develops after a defervescence (table 21).

The number of days from the onset to the last febrile temperature (before cure, death or recognition of complications) was observed over a range of from one to one hundred and fifty-three days (careful study failed to reveal complications in these patients with prolonged fevers), the general average being eleven and one-tenth days. For patients surviving without complication the average was ten and three-tenths days (most frequently seven), for those dying without complication, nine and five-tenths days (most frequently 7), and for all patients with complications, sixteen and two-tenths days (most frequently nine). As the duration of the fever increased there was a definite increase in the complication rate but no great change in the mortality rate (table 21). In table 23 are shown the results of a further study of the total duration of fever. It is clear from this table that the time element is of great importance in determining the character of an unfortunate outcome—whether it will be death or complication or both.

The duration of hospitalization for pneumonia and its sequelae extended over a range of from one to two hundred and seventy days, being from ten to twenty-one days for 39 per cent of the patients. The general average was fourteen and four-tenths days. For patients surviving without complication the average was fourteen and four-tenths days and for those dying without complication four and eight-tenths days, for patients surviving with complication it was forty-one and four-tenths days and for those dying with complication ten and one-tenth

TABLE 22—*Days from Onset to Admission for Patients Without and With Serum, Giving the Number of Patients and the Outcome (per Cent)*

Number of Days From Onset to Admission	No Serum				Serum			
	Number of Patients	Outcome (%)			Number of Patients	Outcome (%)		
		Opti- mum	Death	Compli- cation		Opti- mum	Death	Compli- cation
1 to 3	394	65	22	18	284	75	12	18
4 to 6	279	68	23	13	186	62	22	23
7 and over	200	59	28	26	94	51	34	30

TABLE 23—*Rate (per Cent) of Complication Among Patients Who Died and of Deaths Among Those with Complication, According to Days of Fever from Onset to Complication or Death*

Total Days of Fever	Complication (%) Among Those Who Died	Death (%) Among Those with Complication
0 to 4	8	25
5 or 6	13	27
7 or 8	21	50
9 or 10	32	31
11 or 12	21	21
13 or 14	40	21
15 to 19	30	29
20 to 29	68	42
30 and over	80	30

days (table 21). During 1937 and 1938, the average daily cost per inpatient in this hospital was \$4.71, on that basis alone patients surviving with complications cost about \$127 more per patient than did those surviving without complication—a figure that fails to take into account special services demanded by complications.

A section of table 21 is given to treatment. It is impossible to draw from those data any conclusion concerning the relative or absolute merits of sulfanilamide,¹⁰ oxygen and serum. Much more detailed study is required, this having been attempted for serum in an investigation reported on in another paper.

10 In the only patient to receive sulfapyridine meningitis had already developed

SUMMARY

The records of 1,469 patients with pneumococcic pneumonia were analyzed in an effort to determine the character of pneumonia caused by the various types of pneumococcus and the effect of certain variables in the patient and in the febrile course of the disease on the outcome. A brief study of the complications was also conducted. The effect of concomitant conditions and of serum therapy will be investigated and reported in subsequent papers.

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PNEUMOCOCCIC PNEUMONIA

ANALYSIS OF THE RECORDS OF 1,469 PATIENTS TREATED IN THE
LOS ANGELES COUNTY HOSPITAL FROM 1934 THROUGH 1938

II OUTCOME AND CHARACTER OF PNEUMONIA IN THE PRESENCE
OF ASSOCIATED OR CONCOMITANT CONDITIONS

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LOS ANGELES

Among the variables¹ which determine the character and outcome of pneumonia, one of the most important is the presence of concomitant conditions. In this paper are published the results of a study of the records of 1,469 patients, in 742 of whom some associated or concomitant condition was recognized.

MATERIAL AND METHODS

A concomitant condition is considered as any condition, barring pneumonia and its sequelae, the presence of which was indicated by any part of the patient's record. (If the records had been ideally complete, there would have been few if any patients without such conditions.) The original clinical, laboratory and nursing records of all (1,469) patients with pneumococcic pneumonia from 1934 through 1938 were abstracted in their entirety by some of the group of workers. One of us checked the abstracts with the original records, prepared the data for tabulation and supervised the analysis. Further details are given in the preceding paper.

We disregarded findings and diagnoses qualified by the word "doubtful" or "possible," all changes noted at autopsy that could not (except under the most extraordinary circumstances) be recognized ante mortem and the following miscellaneous conditions (each of which was almost always dwarfed in importance by some additional condition): asymptomatic goiter, asymptomatic prostatic hypertrophy, irregular menses, dysmenorrhea, nonbleeding uterine fibroids, retroversion of the uterus, senile vaginitis, Oxyuria in the urine, nocturia when less than three

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1 A study on the type of pneumococcus, the complications of pneumonia and certain variations in the patient and in the course of the disease has been made on these patients and presented in the first paper of this series.

times a night, "occasional slight jaundice," occasionally bloody stool, permanent colostomy of long standing, small ventral hernia, hydrocele, asymptomatic varicose veins, dental caries, diphtheria carrier, addiction to tobacco smoking, frequent headaches, cataract, parkinsonism, deaf-mutism and absence of patellar reflexes. When two conditions were present one of which was referable entirely to the presence of the first (e g, bronchiectasis and chronic cough), the secondary condition was disregarded. If the conditions were independent, the patient was tabulated once under each condition in the enumeration of the conditions and was disregarded in the study of the character of pneumonia associated with each of the more important conditions. Some effort was made to evaluate the findings statistically, when the term "significant" is used it refers solely to such evaluation.²

OBSERVATIONS

Of the 1,469 patients, 727 were without known concomitant conditions, these formed the "control" group. The other 742 patients had 1,035 concomitant conditions, 523 patients having only 1 and 219 having more than 1 (averaging 2.3 per patient). An enumeration³ of all observed conditions is given in table 1, showing the number of patients with each condition and the outcome (patients with more than one condition appearing once under each). In table 2 are presented data concerning the outcome and character of pneumonia associated with the more common conditions, in patients having only one known condition. The chart indicates the outcomes for certain groups shown in the two tables and (horizontal lines) those for the control group, with the standard errors. The findings concerning the more common conditions are briefly reviewed and discussed in the text.

CONDITIONS OF THE RESPIRATORY TRACT

Patients with histories of two or more attacks of pneumonia did not differ in outcome from patients with present evidence of bronchiectasis, and the two conditions were not infrequently observed together. Such patients were therefore combined to form a group of 45, in 31 of whom no other conditions were recognized. Comparison with the control group shows a significant increase in the optimum outcome rate (survival without complication), a significant lowering of the complication rate and a suggestive lowering of the mortality rate. In patients without other recorded conditions, the pulmonary involvement was less extensive than in the controls. Blood cultures were negative for the 6 patients in whose cases they were made. The apparent difference in racial distribution cannot account for the observed difference in outcome. The ages

2 For example, a "significant" difference in outcome between two groups means that the difference is probably not referable to the small number of patients but implies nothing as regards the other possible causes of the difference, such as age, type of organism and character and number of pulmonary lesions.

3 The conditions are enumerated because they were observed, not necessarily because they are considered important.

TABLE 1—Enumeration of Observed Concomitant Conditions, Showing Total Number of Patients, Number Who Survived Without Complication, Number Who Died and Number in Whom Complications Developed

Concomitant Condition	Total No of Patients	Outcome		
		Optimum	Death	Complication
Respiratory and oral				
"Asthma"	54	36	14	6
Bronchiectasis	14	12	2	0
Bronchogenic carcinoma	2	1	0	1
Chronic cough	57	38	13	8
Chronic laryngitis	1	1	0	0
Chronic sinusitis, otitis media or mastoiditis	21	17	5	7
Congenital pulmonary cysts	1	0	1	0
Deformed thorax	1	1	0	0
Enlarged tonsils	5	4	1	1
Enlarged throat	76	58	10	10
Pneumonia twice or more in the past	1	1	0	0
Pulmonary abscess	31	27	3	1
Recurrent hemoptysis	1	1	0	0
Scattered tubercles	1	1	0	1
Chronic pleurisy or pneumoconiosis	35	20	9	11
Alveolar abscesses	2	2	0	0
Peritonsillar and retropharyngeal abscess	1	0	1	1
Severe tonsillitis	2	2	0	0
Functional "heart" complaints (neurotic ?)	20	8	8	6
Cardiac				
Definite heart disease	163	89	69	30
Compensated	127	74	48	24
Decompensated	36	15	21	6
Auricular fibrillation (? cause)	16	5	10	8
Auricular flutter (? cause)	1	1	0	0
Arteriosclerotic (excluding hypertension)	57	37	19	4
Hypertensive (with or without arteriosclerosis)	50	29	20	7
Rheumatic (chronic)	2	12	10	9
Syphilitic	14	4	9	1
Congenital	1	1	0	0
Subacute bacterial endocarditis	1	0	1	1
Blood				
Anemia				
Secondary	4	2	1	2
Sickle cell	1	0	1	0
Leukemia				
Acute	1	0	1	0
Chronic	2	1	1	1
Dermatologic				
Burns	3	1	2	0
"Dermatitis and stomatitis"	1	0	1	0
Keratosis pilaris	1	1	0	0
Lichen planus	1	1	0	0
Pellagra	1	0	1	0
Psoriasis	1	1	0	0
Varicose ulcers	3	2	1	1
Gastrointestinal				
Appendicitis (no operation)	1	1	0	1
Appendicitis (operation)	4	2	0	2
Inginal hernia (no operation)	2	2	0	0
Peptic ulcer (no operation), 2 bleeding	3	3	0	0
Peritonitis (no operation)	1	0	1	1
Poisoning, saponated solution of cresol, ammonia, arsenic	3	1	1	1
Alcoholism				
Acute	21	11	8	2
Chronic	66	37	26	13
Ulcerative colitis (no operation)	1	1	0	0
Gynecologic and obstetric				
Bleeding uterine fibroids	1	1	0	0
Chronic pelvic inflammatory disease	3	2	1	1
Ovarian cyst (traumatic, twisted, ruptured)	3	1	2	2
Pregnancy				
Not interrupted before pneumonia	17	8	3	8
First trimester	5	4	0	1
Second trimester	7	3	2	2
Third trimester	5	1	1	4
Abortion during course of pneumonia	7	1	2	3
No abortion (or miscarriage or premature delivery)	10	7	0	3
Postpartum (before onset of pneumonia)	12	12	0	0

TABLE 1—Enumeration of Observed Concomitant Conditions, Showing Total Number of Patients, Number Who Survived Without Complication, Number Who Died and Number in Whom Complications Developed—Continued

Concomitant Condition	Total No of Patients	Outcome		
		Optimum	Death	Complication
Hepatic, biliary, and renal (no operation)				
Banti's syndrome	2	1	1	0
Cirrhosis of liver	4	2	2	1
Gallbladder disease				
Acute	1	1	0	0
Chronic	6	2	4	1
Hepatomegaly	2	1	1	0
Jaundice				
Congenital hemolytic	1	1	0	0
Obstructive	2	0	2	0
Infectious (see other headings also)				
"Frequent night sweats"	1	0	1	0
Cellulitis, erysipelas	2	1	1	0
Furunculosis	1	2	1	0
Gonorrhea, acute	4	3	1	0
Malaria, <i>Pl. falciparum</i>	1	1	0	0
Pertussis	1	1	0	0
Rheumatic fever, acute	1	1	0	0
Staphylococci septicemia	1	0	1	1
Syphilis, all evidences	101	61	35	15
Positive serologic reaction only, or treated	73	48	19	11
Syphilitic heart disease	14	4	9	1
Neurosyphilis	4	2	1	1
Other clinical evidences	13	7	6	2
Tuberculosis of femur	1	0	1	0
Varicella	1	0	1	1
Metabolic				
Diabetes mellitus	15	9	4	2
Mild	10	7	1	2
Severe	5	2	3	0
Hyperthyroidism	1	1	0	0
Hypothyroidism	3	2	1	1
Obesity	56	12	17	13
Recent loss of weight	34	26	5	4
Muscular, articular				
Muscular dystrophy	1	0	1	1
Arthritis (not pneumococci)	4	1	3	1
Neoplastic—Carcinoma				
Breast	3	3	0	0
Bronchogenic	2	1	0	1
Cervix uteri	2	2	0	0
Pancreas (head)	1	0	1	0
Prostate	1	1	0	0
Skin	3	2	1	0
Trachea	1	1	0	0
Urinary bladder	1	0	1	0
Neurologic				
Aphasia	1	1	0	0
Cerebral thrombosis	1	0	1	1
Dementia praecox	1	1	0	0
Epilepsy	4	3	1	0
Neurosyphilis	4	2	1	1
Paranoia (congenital psychopathic inferior)	1	1	0	0
Skull fracture	1	0	1	0
Ophthalmologic				
Trachoma	1	1	0	0
Postoperative				
Oral				
Abdominal	11	6	1	4
Intestinal	3	1	2	0
Gastric	4	3	1	0
Appendical	12	11	1	0
Laparotomy	4	3	1	0
Cystostomy or cystotomy	5	2	3	1
Renal	5	5	0	0
Orthopedic	3	1	2	0
Miscellaneous	7	5	1	1
All postoperative	54	37	12	6
All abdominal				
Without peritonitis	16	14	2	0
With peritonitis	7	4	3	0

TABLE 1—Enumeration of Observed Concomitant Conditions, Showing Total Number of Patients, Number Who Survived Without Complication, Number Who Died and Number in Whom Complications Developed—Continued

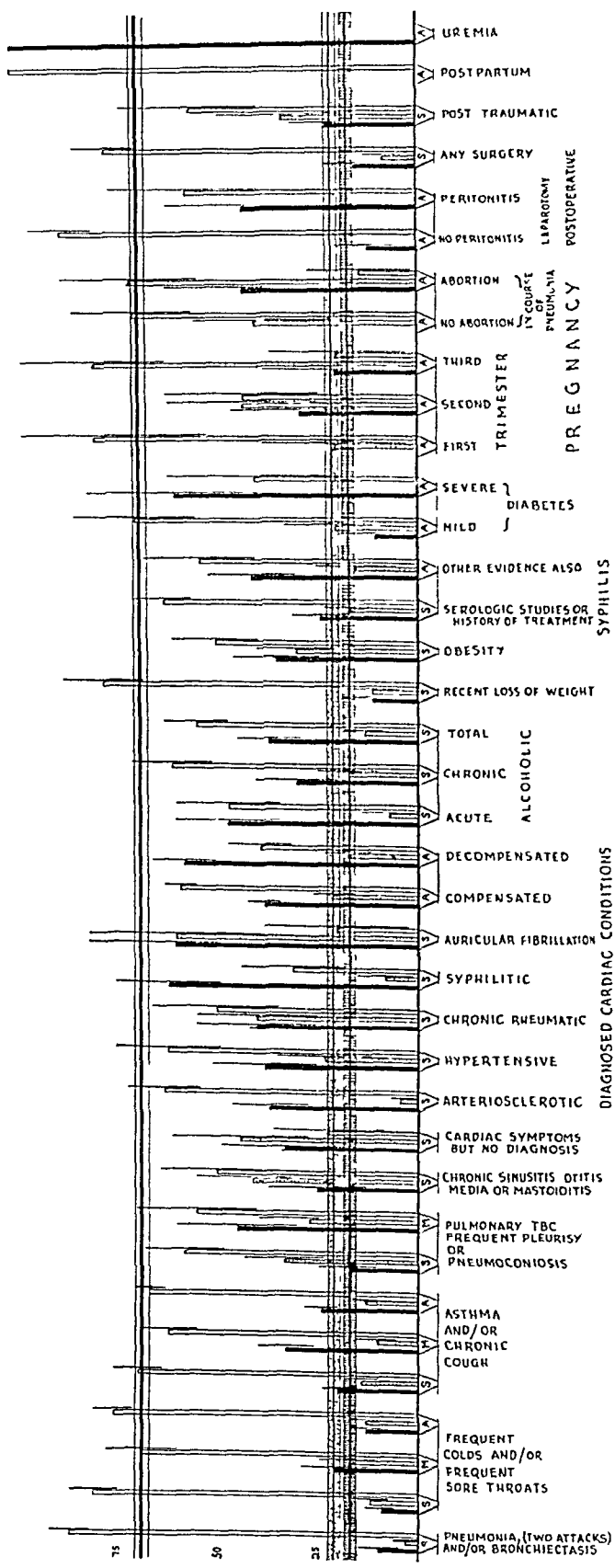
Concomitant Condition	Total No of Patients	Outcome		
		Optimum	Death	Complication
Post traumatic				
Chiefly confined to the thorax	15	9	4	2
Nonthoracic or generalized	7	3	4	1
Renal				
Undiagnosed urinary symptoms	9	6	3	1
Prostatism	4	3	1	0
Cystitis	2	0	2	0
Pyelitis	2	2	0	0
Pyelonephritis	3	0	3	1
Hydronephrosis (with cystitis)	1	0	1	0
Nephrosclerosis				
“Benign”	1	0	1	1
“Malignant”	1	0	1	0
Nephritis				
Acute glomerular	2	0	2	0
Subacute	1	0	0	1
Chronic	1	0	1	0
Uremia	5	0	5	0

* Patients with two or more concomitant conditions are listed once under each

tended to be higher than among the control subjects but lower than among all patients with concomitant conditions. The monthly (not seasonal) incidence was virtually flat except for a sharp peak in mid-winter. Serum was given to the same proportion of these patients as to those of the control group. There were fewer type II pneumococcus due to the infections and more due to the types with higher numbers than there were in the controls, but the differences carry little statistical weight. The improved outcome, the restricted pulmonary involvement and the presumably low incidence of bacteremia cannot be accounted for on the basis of type distribution and indicate that these patients may have had an increased resistance to extension and dissemination of the infection.

Twenty-four patients had pulmonary tuberculosis (the possibility of tuberculous pneumonia was thought to be ruled out), recurrent pleurisy or pneumoconiosis, without other known concomitant conditions. Their mortality was approximately the same as that of the controls, but their complication rate was suggestively elevated and their optimum outcome rate decreased. Types III and VII and the types designated by higher figures predominated. The ages were somewhat higher and the temperatures and leukocyte counts somewhat lower than among the controls. The mortality in the presence of additional concomitant conditions was rather definitely elevated. The presence of tuberculosis or pneumoconiosis or the recurrence of pleurisy in the past probably alters the “resistance” of the patient, making for a higher complication rate in pneumonia.

Patients complaining of “asthma” and of “chronic cough” were not distinguishable on the basis of outcome, and there were many such



CHART

(See legend on opposite page)

patients One hundred and eleven patients presented one or both of these complaints, 69 being without other concomitant conditions. No significant difference existed between them and the controls, though the complication rate was lower, the mortality higher, the ages slightly higher, the fall and winter incidence increased, the leukocyte count and temperature a little lower and the incidence of types I and VIII increased at the expense of types II and III and group IV.

Complaints of frequent infections of the upper respiratory tract, described as colds, sore throats and the like, were made by 76 patients, and there was no other known abnormal condition in 47 of these. The outcome rates were suggestively better than those of the controls in the incidence of types IV, VII and VIII and group IV as well as a decrease in that of types I, II and IX. Lobar lesions were less frequent and less extensive and blood cultures were negative for the 5 patients studied. (These differences carry little statistical weight.) It is possible that localized breaks in the patient's resistance are responsible for establishing the pneumonia, both in patients complaining of frequent infections of the upper respiratory tract and in those with bronchiectasis or recurrent pneumonia, but that the neighboring tissues often have an increased resistance and are able to prevent the local extension or wide dissemination of the organisms.

While only 12 patients presented chronic infections of the sinuses or the ears, without other concomitant conditions, they formed an interesting group. The marked elevation of the complication rate and depression of the optimum outcome rate carried little statistical weight. Although 7 of the 12 received serum, 3 died, 5 had complications and only 6 survived without complication. The abnormalities of the respiratory system just mentioned may be arranged with respect to outcome, from best to worst pneumonia twice or more, and/or bronchiectasis, frequent infections of the upper respiratory tract—colds, sore throats and others, "asthma" and/or "chronic

LEGEND FOR CHART

Chart showing the percentage outcome (with their standard errors) for patients with certain concomitant conditions (vertical bars) and for all patients without known concomitant conditions (as horizontal lines reading from below upward indicating mortality, complication and optimum outcome rates). Optimum outcome is survival without complication. *S* represents patients with a single recognized condition (table 2), *M*, patients with multiple conditions, and *A*, all patients with the indicated condition (table 1). "Heart symptoms but no diagnosis" appears in the tables as "functional 'heart' complaints (neurotic?)", "auricular fibrillation," signifies other heart disease not recognized. Arteriosclerotic-hypertensive heart disease is included in the chart with the "hypertensive" group. The terms "pregnancy" and "postpartum" designate the condition at the onset of pneumonia.

cough", pulmonary tuberculosis, recurrent pleurisy or pneumoconiosis, and chronic sinusitis, chronic otitis media or chronic mastoiditis

FUNCTIONAL CARDIAC COMPLAINTS

Nine patients complained of having had, without relation to the pneumonia, certain symptoms, such as palpitation, dyspnea, precordial pain and ankle edema, which are usually attributed to some abnormality of cardiac function, there were, however, no findings suggestive of car-

TABLE 2—Data on the More Common Concomitant Conditions in Patients Having With and "Without"

Concomitant Conditions in Patients with Only One Known Condition *	Total Number of Patients	Outcome (%)				According to Age				Sex, Percentage Male
		Optimum	Death	Complication	Percentage Treated with Serum	1 to 19	20 to 39	40 to 59	60 and Over	
Pneumonia twice or more in the past and/or bronchiectasis	31	87	10	3	39	13	26	45	16	65
Frequent colds and/or sore throats	47	81	9	12	30	21	56	11	11	72
"Asthma" and/or chronic cough	69	70	19	14	48	9	48	33	10	57
Pulmonary tuberculosis, recurrent pleurisy, pneumoconiosis	24	68	17	33	38	0	29	59	13	62
Chronic paranasal or aural infection	12	50	25	41	58	8	66	25	0	25
Functional "heart" complaints (neurotic?)	9	22	33	44	56	0	22	33	44	44
Arteriosclerotic (excluding hypertension) heart disease	27	63	37	4	22	0	0	22	78	74
Hypertensive (with or without arteriosclerosis) heart disease	13	62	38	23	8	8	16	16	62	54
Chronic rheumatic heart disease	10	50	40	40	0	10	40	50	0	30
Syphilitic heart disease	13	31	62	8	15	0	8	31	62	69
Alcoholism Acute	15	47	47	7	33	0	47	40	13	87
Chronic	23	61	30	17	39	0	52	43	4	83
Recent loss of weight	18	78	11	11	67	17	33	44	6	72
Obesity	20	50	35	30	40	5	25	40	30	31
Positive Wassermann reaction or therapy in past	46	63	24	17	28	4	50	39	7	76
Pregnancy	12	42	25	50	42	8	83	8	0	0
Postoperative	26	77	15	8	38	31	54	12	4	58
All patients in whom one or more concomitant conditions were Present	742	63	28	17	36	8	37	33	21	62
"Absent"	727	69	17	21	41	19	45	29	8	68

* Certain conditions were combined and considered the same if fundamentally allied, not differing in outcome and often concurrent

† Arable figures indicate Cooper types, IV signifies group IV (in use until the latter part of 1936, when classification of types 4 to 32 was introduced)

‡ "Atypical" includes only lesions definitely atypical ante mortem or possibly atypical lesions found atypical at autopsy

diovascular disease Under such circumstances it is not uncommon to pass over the complaints as evidences of neurosis in the patient or of overzealous prodding by the elicitor of the history We were surprised to find that of the 9 patients only 2 survived without complication, 3 died and 4 had complications In spite of the small number of patients, the differences between these rates and those of the controls carry considerable statistical weight The extent of the change in outcome can be accounted for only with extreme difficulty on the basis of the higher age distribution or the greater number of infections of more than one

Only One Recognized Condition and Similar Data for All Patients Concomitant Conditions

§ The "number of patients" signifies the number for whom total leukocyte count was made during acute illness. The distribution is according to the maximum recorded count, in thousands of cells.

|| The maximum temperature during the first few hours in the hospital is given. By total days febrile is meant the number of days from onset to the last temperature above 99 F before cure, death or the recognition of a complication.

CARDIOVASCULAR DISEASES

It is especially in the presence of cardiovascular diseases that the pneumonias are confusingly classified. If the heart is compensated, the pneumonia is generally assumed to be "primary" and the significance of the cardiac disease is minimized, if decompensation precedes the onset of pneumonia, the latter is usually called "secondary" or "terminal" and is often considered to be of relatively little importance, while if decompensation commences during the course of pneumonia, it is often looked on as a physiologic complication of pneumonia. Valid as that

classification may be, it offers considerable opportunity for misrepresentation

Arteriosclerotic (nonhypertensive) heart disease was the only concomitant condition recognized in 27 patients, other conditions being noted in 30, making a total of 57. Comparison of patients having the single condition with the control subjects shows the optimum outcome rate unchanged, the mortality rate suggestively higher and the complication rate significantly lower (4 per cent). All the patients were over 40 years of age, and most were over 60. Controls of the same age had considerably higher death and complication rates than did the patients with arteriosclerosis, among whom there was a somewhat lower incidence of the more virulent types (half being types IX to XXXII and the other half I to VIII and group IV). More than half the lesions were atypical, and most of the lobar forms were limited to one lobe. The leukocyte count was somewhat lower, and the temperature on admission decidedly lower, than for the controls (of the same or of all ages). It is clear that the arteriosclerotic patients had an exceedingly low complication rate, as judged by any standard, and a mortality rate lower than for controls of the same age, while the pneumonias tended to be due to organisms designated by higher figures, to be atypical or limited in extent and to give rise to lower temperatures.

Hypertensive heart disease, with or without arteriosclerosis, was noted in 50 patients, in 13 of whom additional conditions were not recognized. The outcome among the 13 patients was apparently worse than that among the controls, but the difference carries little statistical weight. Only 1 of the patients received serum. Types III, V, VII and IX and group IV were represented. The age distribution and the temperature on admission were intermediate between those for the arteriosclerotic patients and those for the controls. In 12 of the 13 patients the disease developed during the winter "peak" months. Presence or absence of noncardiac conditions being disregarded, it was found that in the absence of decompensation the outcome was suggestively worse among the hypertensive than among the arteriosclerotic patients but that in the presence of decompensation there was no difference in the outcomes in the two groups.

Chronic rheumatic heart disease was diagnosed as occurring in 23 patients, 10 of whom had no other known concomitant condition. The outcome was suggestively worse than that among the controls. The 10 patients were characterized by a rather high incidence of extensive lobar lesions, a "normal" leukocyte count for half the studied patients, a relatively low temperature and a high incidence of women. These patients may be compared with the arteriosclerotic ones. The two groups had equal mortality rates, but the complication rate among the arteriosclerotic

patients was very suggestively lower. On the basis of the observed type distributions (control subjects being used as a measure), one would expect a complication rate of 16 per cent for the arteriosclerotic and 17 per cent for the rheumatic patients. The differences in age, sex and race were similarly inadequate to account for the observed difference in the complication rates. The effect of decompensation on the complication rate was virtually nil. Differences in the pulmonary involvements of the two groups would lead one to expect a 2 per cent difference in the complication rates. We are inclined to ascribe the difference to barriers against the spread of the pneumococci in the arteriosclerotic patients—probably on the basis of vascular and lymphatic sclerosis.

Syphilitic heart disease was definitely worse than in the controls (8 died, 1 had a complication and 4 survived without complication). The general characteristics of pneumonia in the presence of syphilitic heart disease were similar to those in the presence of hypertension, the apparently considerable difference in outcome carrying little statistical weight. In the patients with syphilis the low complication rate may have been a reflection of a very high mortality rate.⁴ To what extent the poor outcome may have been due to the ravages of syphilis in other organs, such as the liver, cannot be estimated. It is interesting to compare patients with noncardiac syphilis with these patients or who were 73 patients on whom serologic studies gave positive results or who had a history of recent treatment, and in whom no other stigmas were found, 4 patients with neurosyphilis, 13 with additional evidence of syphilis (excluding cardiac and neurologic evidence), and the aforementioned patients with cardiac disease. For each of the groups the mortality was greater than for the controls, and the mortality rose from group to group when they were listed in the order just given. The incidence of complications was not impressive.

Auricular fibrillation is an extremely interesting condition in the presence of organic heart disease. It is usually looked on as a complication of that disease, in the absence of known heart disease it is considered as a "complication" of pneumonia (this has not been done in these papers), due either to embarrassed pulmonary circulation or (more probably) to profound "toxemia"—delirium cordis and delirium mentis being placed on the same basis. It is appar-

⁴ This argument rests on the contention that the course was abbreviated in about two thirds of the patients, so that insufficient time was available for the development of complications. If the patients had lived somewhat longer they might have died with rather than without complications or might have had complications but survived. (These variations in the outcome—fatality without complication, fatality with complication and survival with complication—may take place without affecting the optimum outcome rate.)

ent that proper classification demands knowledge of the ease with which the heart could be made to fibrillate in the absence of pneumonia and of the ease with which pneumonia could cause a normal heart to fibrillate. These questions are unanswerable, so far as we know, and we have therefore followed general practice by including patients with auricular fibrillation among those with the already mentioned cardiac conditions whenever possible. We present here a group of 16 patients without other known cardiac disease (additional, noncardiac concomitant conditions were present in 11). The disease was severe in these patients and the outcome was significantly worse than in the controls. Only 31 per cent of the 16 patients survived without complication, 50 per cent had complications, and 63 per cent died, 44 per cent of the patients dying with complications.

In all, there were 163 patients with organic heart disease, in 36 of whom evidences of cardiac insufficiency were found. Decompensation was accompanied by a higher mortality and a lower optimum outcome rate than was compensation (the differences being rather significant) but there was no difference in the complication rates. The character of the underlying cardiac disease seems to have been of little importance in the presence of decompensation.

OTHER DISORDERS

Eighty-seven patients suffered from alcoholism (excluding patients described as minimal imbibers), in 38 of whom other concomitant conditions were not reported. Of the latter group, 23 had chronic alcoholism and 15 acute. The mortality rate was greater than in the controls, but the lowering of the complication rate carried little statistical weight. As regards the outcome, there was no significant difference between the patients with the acute and those with the chronic form of the disease. A short febrile course in those having acute alcoholism was due to early deaths. Pneumococci of types I, II, III and VII occurred in 57 per cent of the controls, in 48 per cent of all patients with concomitant conditions in 43 per cent of those with chronic alcoholism and in 28 per cent of those with acute alcoholism.

A recent loss of weight was noted in the histories of 34 patients, 18 of whom were without other abnormal conditions. The observed improvement in outcome carried no statistical weight (the odds being about 5 to 1 that the difference was not due solely to chance). Of 56 patients showing obesity, 36 had other conditions as well. Most of the remaining 20 patients were women and over 40 years old, their mortality was rather significantly elevated, but their complication rate was the same as that of the controls. Obesity was not in these patients a particularly grave concomitant condition.

Though there were few patients with diabetes mellitus they presented interesting findings. In the absence of coma or excessively high blood sugar levels (10 patients) the outcome was no worse than in the controls, but among the 5 patients with severe diabetes the mortality was suggestively higher than among either the patients with mild disease or the controls. The pneumonia tended to be atypical and not particularly extensive. All the patients were febrile ten days or less before cure, death or recognition of complications, there being no other group with such a short course.

Pneumonia was superimposed on pregnancy in 17 patients, other conditions being "absent" in 12. Abortion (including miscarriage and premature delivery) occurred during the course of the pneumonia in 7 of the 17. In the absence of abortion death did not occur, but a third of the patients had complications (of the pneumonia). When abortion occurred during the pneumonia, the mortality and the complication rate rose to high levels and the optimum outcome rate fell to a minimum. The outcome became progressively worse with increasing duration of the pregnancy, but this reflected an increasing incidence of abortion. The general elevation of the complication rate cannot be ascribed entirely to the type distribution. It is probable that the occurrence of abortion was an indication of the severity of the pneumonia. We feel that it is possible that pregnant women are unusually resistant to pneumonia, that when they do become infected the disease is frequently due to one of the more virulent types of pneumococcus, that if abortion can be avoided the patients are more than usually able to cope with the "toxemia" of pneumonia and to survive, but are not particularly resistant to the development of complications, that the chances of abortion increase with the duration of the pregnancy, and that if abortion does occur during the pneumonia the mortality and the complication rate rise to high levels. In suggesting that the resistance is increased, we have considered further evidence presented by 12 postpartum patients in whom pneumonia developed: all survived without complications.

Post-traumatic or postoperative pneumonia was found in 80 patients. Patients in whom pneumonia developed after general trauma (as from automobile accidents) had a suggestively higher mortality rate than the controls. The outcome in all patients with postoperative pneumonia was not statistically different from that in the controls. No complications occurred in 24 patients with pneumonia following laparotomy, but in the presence of peritonitis the mortality was elevated.

Eighteen patients had various forms of disease of the liver or biliary tract, 58 per cent of them died (a highly suggestive increase in mortality over that of the controls). Some form of renal disease (excluding prostatism) was diagnosed as present in 13 patients. 1 of the 3 who

survived (subacute nephritis) and 2 of the 10 who died had complications (uremia occurred in 5 of those who died) These concomitant diseases are thought to have been present before the onset of the pneumonia The deplorable outcomes may indicate the importance of the liver and kidneys in the natural defenses against pneumonia

COMPARISON OF THE TWO GROUPS OF SUBJECTS

The 742 patients with concomitant conditions may be compared with the 727 controls In the former group there was an impaired outcome, a higher death rate, a lower optimum outcome rate and a suggestively lower complication rate The incidence of types I and II was decidedly diminished, while the incidence of types III, IV, V, VIII and those designated by higher figures was slightly increased The pulmonary involvement was much more often atypical but was no less extensive The temperature on admission tended to be somewhat lower, but the febrile course was not abbreviated The patients were definitely older, on the average, the sexes were more equally represented, and there were fewer Mexicans (owing, perhaps, to difficulties in eliciting complaints pointing to concomitant conditions) Bacteremia was more frequently found when looked for, but there was no difference in the leukocyte count

SUMMARY AND CONCLUSIONS

The records of 1,469 patients with pneumococcic pneumonia were examined in an effort to learn the effect of the presence of certain concomitant conditions on the outcome and character of the pneumonia All observed conditions are noted, the most frequent or important being discussed

Mary C Moore and Josephine Abraham lent valuable assistance in the analysis of data

MULTIPLE PRIMARY MALIGNANT LESIONS OF THE LARGE BOWEL

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Multiple primary malignant lesions of the large intestine have been reported occasionally. A number of factors have made this study seem timely: (1) the bearing that this syndrome may have on the problem of cancer in general, (2) the great importance that these multiple tumors may possess in respect to the prognosis for patients who have malignant lesions, (3) the relative paucity of attention that multiple malignant lesions of the large bowel have received, and (4) the relationship that polyps bear to the pathogenesis of malignant lesions of the large bowel.

Ewing,¹ Hanlon² and Orr³ stated the belief that multiple primary malignant lesions are merely coincidental occurrences. Warren and Gates⁴ have not expressed the same opinion, and a study of the cases reported in the present paper would draw us also away from such an opinion. Maud Slye⁵ was able to demonstrate that "in mice resistant by heredity, irritations and traumas incident to life in this laboratory have never been able to induce cancer, while in mice susceptible by heredity to only one location of cancer, irritations or stimulations applied to other parts of the body have to date failed to induce neoplasms in these insusceptible tissues." Her ability to breed into mice as well as to breed out of mice the tendency, not alone toward malignant disease in general, but also toward specifically localized tumors, seems to indicate that some

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1 Ewing, J. Neoplastic Diseases, ed 3, Philadelphia, W B Saunders Company, 1928, p 37

2 Hanlon, F R. Multiple Primary Carcinomas, *Am J Cancer* **15** 2001-2012 (July) 1931

3 Orr, J W. Multiple Malignant Neoplasms, *J Path & Bact* **33** 283-290 (April) 1930

4 Warren, S, and Gates, O. Multiple Primary Malignant Tumors. A Survey of the Literature and a Statistical Study, *Am J Cancer* **16** 1358-1414 (Nov) 1932

5 Slye, M. The Relation of Heredity to the Occurrence of Cancer, *Radiology* **29** 406-433 (Oct) 1937

inheritable biologic factor influences the destiny of a group of tissues. There are many clinical observations at hand which gave support to Slye's work.

It has been noted that multiple cancers occur in various tissues of the same person and at various sites in the same organ, such as the large intestine. Furthermore, a tendency to such occurrences has been encountered among various members of families through several generations.

In the past, the decision as to whether two lesions were independent of one another rested on Billroth's postulates, namely: 1. The two growths must show distinct histologic differences. 2. Each growth must spring from its parent epithelium. 3. Each growth must be held responsible for its own metastatic lesions. Mercanton⁶ added still another condition when he pronounced that the independence of the growths from one another is assured if the patient remains free from disease after the removal of the second lesion.

The criteria suggested by Warren and Gates are more applicable to lesions in the same organ, and the fulfilment of certain conditions was a prerequisite to the inclusion of multiple lesions in their series. These conditions are: (1) Each tumor must be malignant, (2) each growth must be distinct, and (3) one lesion cannot be a metastatic implant from the other.

In the past, transplantation from one site in the bowel to another was thought to explain the occurrence of more than one lesion. Transplantation of carcinoma in the large bowel from one site to another is extremely rare. Transplantation by way of the lumen would fail entirely to explain those cases in which the proximal growth is smaller than and far separated from the distal growth. Furthermore, the mucus secreted in the large bowel, the peristaltic activity of the bowel and the force of the fecal stream probably would not allow the cells cast off from one growth to grow at a distal site. Implantation of cancer cells no doubt occurs at some sites, notably in cases of Krukenberg's tumors of the ovary, but this is not the correct explanation for the multiple growths in the large bowel. Robertson,⁷ after an extensive experience, has remarked that carcinomatous transplantation in the large intestine must be extremely rare.

6 Mercanton, F, cited by Miller, R. T., Jr. Multiple Primary Malignant Foci in Cancer of the Colon, *Ann Surg* **80** 456-472 (Sept.) 1924.

7 Robertson, H. E. (a) Personal communication to the authors, (b) Polyps of the Colon and Their Possible Significance, *Bull Am Soc Control Cancer* **16** 6-7 (Feb.) 1934.

We have gathered 23 cases from the records of the Mayo Clinic since the report by Rankin and one of us (Bargen⁸) was made and have divided them into two groups (1) those in which multiple cancers occur simultaneously (synchronous) and (2) those in which multiple cancers occur at different times (metachronous). We have excluded from this series of cases instances of multiple polyps of low grades of malignancy and of single lesions that grossly were undoubtedly carcinomatous and that were associated with single polyps of a low grade of malignancy. Such cases may belong in a group of cases of multiple primary neoplasms, but the divergence of opinion at this time precludes such a classification. The single or multiple occurrence of polyps with cancer of the large intestine is common. If these polyps are precancerous lesions, why is there a great variation between the incidence of polyps and that of cancer? It would seem that part of this discrepancy can be accounted for by the fact that many patients who have polyps in the large bowel die from other causes before the polyps have had time or sufficient stimulation to become malignant. The interpretation of the microscopic structure of polyps of the "borderline" variety is dependent on the variables of past training and personal convictions. Polyps labeled adenocarcinoma of grade 1 may well be termed "benign" by some. Whether any particular growth of this description will eventually in carcinoma can only be conjectured. Too many unknown and unpredictable elements are involved in such a question. It is certain, however, that not all polyps will become liabilities to their hosts.

REPORT OF CASES

GROUP I

CASE 1—A man aged 58 years came to the clinic on Sept 16, 1931, he complained of pain in the rectum and bloody stools of six months' duration. Three months before admission morning diarrhea had begun, together with tenesmus and bloody stools.

Examination, disclosed an annular carcinoma in the proximal half of the rectum. At operation, colostomy was performed and a second lesion was found in the sigmoid flexure. The pathologic report was colloid adenocarcinoma of the rectum of grade 3, measuring 9 by 6 by 2.5 cm, and annular adenocarcinoma of the sigmoid flexure of grade 2, measuring 6 by 5 by 1.5 cm. The lymph nodes were not involved.

CASE 2—A man aged 54 years came to the clinic on Aug 20, 1937, he complained of a sensation of pressure in the lower part of the abdomen, relieved by voiding. This distress gradually became more severe and was associated with malaise and some nausea. About one month before his arrival at the clinic, this pain became localized in the left lower abdominal quadrant and a questionable mass appeared in that region. During the three weeks preceding admission, the patient had lost 16 pounds (7.3 Kg).

⁸ Bargen, J. A., and Rankin, F. W. Multiple Carcinomata of the Large Intestine, *Ann Surg* 91:583-593 (April) 1930.

Examination revealed a large, firm, tender mass in the left lower abdominal quadrant. Roentgenologic examination revealed changes suggestive of a perforating carcinoma of the descending colon. Pathologically there were two lesions. The more proximal lesion was adenocarcinoma, grade 2, which measured 2.5 by 2 by 1 cm, the more distal lesion was polypoid adenocarcinoma, grade 3, which measured 3 by 3 by 1 cm. The lymph nodes were not involved.

CASE 3—A man aged 55 years came to the clinic on Dec 12, 1929. For eight years this patient had noted a passage of blood with hard stools. During the eight weeks that preceded his admission there had been a frequent desire to defecate, often resulting only in the passage of flatus and a little blood. The patient remarked that he had felt "as though he were blocked." The caliber of the stools had diminished recently and the patient had lost about 10 pounds (4.5 Kg).

Examination disclosed two lesions in the rectum. The pathologic report was adenocarcinoma of the lower part of the rectum, grade 2, measuring 3 by 3 by 1.5 cm, and polypoid adenocarcinoma of the upper part of the rectum, grade 2, measuring 2 by 2 by 1 cm.

CASE 4—A woman aged 43 years came to the clinic in January 1933, with a history of having noted a little blood in the stools for one year. During the six months that preceded her admission, she had been severely constipated and had been aware of an aching soreness in the rectum.

Examination revealed a large cauliflower-like lesion on the posterior rectal wall. The pathologic report was polypoid, ulcerating adenocarcinoma of the rectum, grade 2, measuring 6 by 5 by 2 cm, with extensive involvement of a vessel, probably a vein, and surrounding connective tissue. A second primary growth was found 7 cm proximal to the lesion, adenocarcinoma, grade 2, with shallow ulceration.

CASE 5—A man aged 45 years came to the clinic on Dec 7, 1936. For three years preceding his admission the patient had suffered from recurring episodes of diarrhea, with the passage of four to six watery stools each day for three or four days. Between these episodes of diarrhea, the bowel habits were entirely normal. For six months prior to admission the patient had had a sensation of not completely emptying the rectum, and in addition to one or two normal stools daily he would pass three or four bloody, mucoid rectal discharges.

Examination disclosed a lesion in the rectum. At operation, a second growth was found in the descending colon. The pathologic report was ulcerating adenocarcinoma of the descending colon, grade 2, measuring 6 by 5 by 1 cm. The lesion in the rectum was an adenocarcinoma of grade 1. In addition, this patient also had an epithelioma of the penis.

CASE 6—A man aged 45 years came to the clinic in 1914, he complained of intercostal neuralgia. For some time he had passed a little mucus in the stools, but the bowel movements otherwise had been normal.

Examination revealed a polyp 12 cm from the anal margin without ulceration. The patient was urged to have this growth removed but he refused. He returned on Oct 16, 1930 and stated that for one year prior to this date an already chronic constipation had become increasingly severe and in addition that he had passed a little blood with the stools. For two months preceding his admission there had been a progressive loss of strength and a loss of 18 pounds (8.2 Kg). In August 1930 a colostomy had been performed, elsewhere. Since that time, bleeding had increased, and the patient passed four to eight bloody rectal discharges daily.

Examination revealed a large annular mass in the middle third of the rectum, with marked fixation and obstruction. Just distal to the growth, there was another flat malignant lesion. The pathologic report was adenocarcinoma of the rectum, grade 2, measuring 8 by 6 by 3 cm, 2 cm distally a second lesion was found, adenocarcinoma, grade 3, measuring 1.5 by 1 by 5 cm. The lymph nodes were not involved.

CASE 7—A man aged 70 years came to the clinic on Aug. 9, 1937 and related a history of having five to nine unformed bowel movements daily for three years. Blood had not been present in any of the rectal discharges.

Examination revealed a polypoid lesion on the anterior rectal wall. Roentgenologic examination disclosed an annular lesion in the descending colon at the level of the iliac crest. The pathologic report was ulcerating adenocarcinoma of the descending colon, grade 2, measuring 4 by 3 by 1 cm, and adenocarcinoma of the rectum, grade 1, measuring 7 by 5 by 2 cm. Lymph nodes were not involved.

CASE 8—A man aged 59 years came to the clinic on Aug. 12, 1937, he related a history of having passed bloody, mucoid rectal discharges for three years and at times only bloody mucus. For two years preceding his admission, the patient had noted a diminishing caliber of the stools, they gradually became soft, then watery and finally more frequent—five to seven stools daily.

Examination revealed a mass in the rectum, the sigmoid flexure was firm, tender and irregular. Proctoscopic examination revealed an annular, ulcerated lesion 9 cm from the anus, it involved the proximal third of the rectum and caused severe obstruction and fixation. The pathologic report was adenocarcinoma of the rectum, grade 3, measuring 3 by 3 cm, distal to the other lesion was an adenocarcinoma, grade 2, measuring 7 by 7 by 3 cm. Lymph nodes were not involved. This patient also had a squamous cell epithelioma of the urinary bladder, grade 3.

CASE 9—A woman aged 41 years came to the clinic on Nov. 15, 1937 and related a history of rectal urgency and bleeding of one year's duration. During the six months preceding her admission, there had been bloody mucoid discharges and the passage of two or three formed stools daily.

Examination revealed a lesion in the sigmoid flexure. Just above the anus on the anterior rectal wall was a second lesion, 3 to 4 cm long. The pathologic report was annular ulcerating carcinoma of the sigmoid flexure, grade 2, measuring 5 by 5 by 3 cm, and adenocarcinoma of the distal part of the rectum, grade 1. The lymph nodes were not involved.

CASE 10—A woman aged 50 years came to the clinic on Sept. 15, 1937. Since 1903, this patient had suffered from sour stomach and acid eructations. Three years preceding her admission these symptoms became aggravated. There was a feeling of fullness after meals and occasional vomiting, and at that time the first attack of dull pain occurred in the right upper abdominal quadrant. Since then, there had been several similar attacks, usually accompanied by nausea and vomiting. Six months before admission, the patient had begun to pass two watery stools daily, although previous bowel habits had always tended toward constipation. During the six months before admission to the clinic, there had been a loss of 30 to 40 pounds (13.6 to 18.1 Kg). Examination revealed a filling defect in the cecum and ascending colon and a small "polyp" on the right rectal wall. The pathologic report was ulcerating adenocarcinoma of the cecum, grade 2, measuring 6 by 5 by 2 cm, and polypoid adenocarcinoma of the ascending colon, grade 2.

measuring 3 by 4 by 2 cm. These lesions were 3 cm apart. There was some involvement of lymph nodes.

CASE 11—A woman aged 56 years came to the clinic on Sept 8, 1937. This patient had been well until January 1936, when she had suffered from an attack of intestinal obstruction. Since July 1936 there had been intermittent attacks of a low grade of obstruction, with only occasional rectal discharges. Examination revealed the obstruction to be in the sigmoid flexure. The pathologic report was ulcerating, perforating carcinoma of the sigmoid flexure, grade 2, measuring 4 by 3 by 3 cm, ulcerating adenocarcinoma of the sigmoid flexure, grade 2, measuring 3 by 3 by 3 cm, and ulcerating, perforating adenocarcinoma of the sigmoid flexure, grade 2, measuring 3 by 3 by 2 cm. There was some involvement of lymph nodes.

CASE 12—A woman aged 59 years came to the clinic on Jan 31, 1935, complaining of general weakness and anemia for six months. During this time, there had been generalized abdominal pains resembling the pains of labor. During the four weeks preceding admission, there had been some rectal urgency and the passage of flatus or bloody mucus. Also, there had been slight pain in the rectum accompanying bowel movements.

Examination revealed a lesion in the sigmoid flexure and another in the ascending colon. The pathologic report was papillary adenocarcinoma of the sigmoid flexure, grade 2. Involvement of lymph nodes was not found. The patient died after anterior resection of the sigmoid flexure was performed. The presence of the lesion of the ascending colon was confirmed.

CASE 13—A woman aged 59 years came to the clinic on Nov 29, 1937, she related a history of having suffered from gas pains and the daily passage of one or two mushy stools without blood.

Examination revealed a defect in the transverse colon. At exploratory operation colloid adenocarcinoma of the cecum, grade 1, measuring 6 by 5 by 2 cm, with serosal involvement, and ulcerating colloid adenocarcinoma of the transverse colon, grade 1, measuring 8.5 by 5 by 1 cm, were found. The mucosa between the two lesions was studded with adenomatous polyps 1 to 2 cm in diameter, many of which were adenocarcinoma of grade 1.

CASE 14—A woman aged 39 years came to the clinic on Dec 3, 1936, she related a history of having had for ten months prior to admission recurring constipation and diarrhea with the passage of eighteen to twenty bloody, mucoid stools daily. Such episodes were accompanied by abdominal cramps and distention, and the associated vomiting persisted for seven to fourteen days. One month preceding her admission, the patient had suffered from an attack of severe abdominal pain with almost persistent vomiting and a failure to pass either flatus or stool for twenty-four hours. During the three months before her arrival at the clinic, the patient had noticed an inability to retain more than 8 ounces (240 cc) of fluid in the rectum.

Examination disclosed a large annular ulcerating lesion of the rectosigmoid, with severe obstruction. Below the lesion were a number of sessile polyps. Because of the severe obstruction, exploration was not attempted at the time that colostomy was performed. Three weeks postoperatively, a cystic tumor was noted in the right lower abdominal quadrant. This was accompanied by recurring signs of obstruction. At the time of the second operation, a mass was found in the transverse colon just distal to the hepatic flexure. This mass was the size of an orange and was producing almost complete obstruction. It was removed. The pathologic

report was colloid adenocarcinoma of the hepatic flexure, grade 3. Glandular involvement was not noted. At the time of the combined abdominoperineal resection, an adenocarcinoma, grade 1, of the proximal part of the rectum was removed, it measured 3 by 2 by 1.5 cm. Distal to this there was a colloid adenocarcinoma, grade 2, that measured 6 by 5 by 1.5 cm. In the rectum and sigmoid flexure there also were a number of adenomatous polyps, pedunculated and sessile, ranging in diameter from 1 mm to 1 cm.

CASE 15—A woman aged 48 years came to the clinic on Aug 20, 1934. She had been well until the winter of 1933-1934, when she first experienced abdominal discomfort accompanying bowel movements. In the spring she began having five to six bloody mucoid stools daily and considerable rectal pain. The patient had lost about 10 pounds (4.5 Kg).

Examination revealed an indurated mass high in the rectum. At operation colostomy was performed and a second mass was discovered in the sigmoid flexure. The pathologic report on the resected lesion of the sigmoid flexure was colloid adenocarcinoma, grade 2, with involvement of lymph nodes, grade 2. The lesion in the rectum was adenocarcinoma, grade 2.

CASE 16—A man aged 55 years came to the clinic on May 27, 1926, he complained of colicky pains in the hypogastrium, mostly on the left side and usually more severe about twenty minutes after meals. This distress was relieved by a bowel movement. During the six months preceding the onset of these symptoms constipation had increased, and during the three months preceding his admission to the clinic the caliber of his stools had diminished. At no time had there been blood, pus or mucus.

Examination revealed an elongated, tender mass in the left lower abdominal quadrant. At operation a tumor was found in the sigmoid flexure. The pathologic diagnosis was adenocarcinoma of the sigmoid flexure, measuring 6 by 4 by 1.5 cm. Lymph nodes were not involved. There was also a polypoid soft growth in the posterior rectal wall. The patient was urged to have this removed, but refused. On Sept 20, 1933 he was readmitted to the clinic because of a recent increase in the amount of mucous discharge from the rectum and occasional, slight, bloody discharge. There had also been a bearing down feeling and a sense of fulness in the rectum. Examinations revealed a large polypoid mass on the right posterior rectal wall. The pathologic report was polypoid adenocarcinoma of the rectum grade 1, measuring 4 by 6 by 4 cm. The lymph nodes were not involved.

GROUP II

CASE 17—A woman aged 44 years came to the clinic on June 17, 1933. This patient had had a resection of the transverse colon performed elsewhere in 1921 for carcinoma. She had remained well until six months before her admission when general weakness developed. Two months preceding admission a mass was discovered in the right lower abdominal quadrant, and since that time there had been some diarrhea without blood. In the six months preceding admission the patient had lost 45 pounds (20.4 Kg).

Examination revealed filling defects in the cecum and ascending colon. Surgical resection was undertaken. The pathologic report was colloid adenocarcinoma of the ascending colon, grade 2, measuring 5 by 5 cm, and colloid adenocarcinoma of the cecum, grade 2, measuring 6 by 6 cm. The lymph nodes were involved.

CASE 18—A man aged 46 years came to the clinic in November 1901 and was operated on for carcinoma of the cecum. He returned, at the age of 78, on Feb 11

1933 Nine months preceding his second admission, he had experienced sharp pains over the entire abdomen, with a sense of fulness after meals, increasing constipation and occasional rectal bleeding. One week preceding admission, signs of comparatively severe intestinal obstruction had developed. A resection of the sigmoid flexure was performed, and the pathologic report on the resected specimen was annular adenocarcinoma of the sigmoid flexure, grade 2, measuring 3 by 3 by 1 cm. The lymph nodes were not involved.

CASE 19—A man aged 50 years came to the clinic on Sept 7, 1933. Three years preceding his admission, a diagnosis of peptic ulcer was made because of epigastric distress. Beginning two years before admission, there had been abdominal pain accompanied by vomiting one hour after meals and persisting three or four hours, occurring every four or five weeks. These symptoms had increased in frequency and severity. Colostomy was performed elsewhere for obstruction.

Examination at the clinic revealed a lesion in the cecum. The pathologic report on the resected specimen was annular, ulcerating adenocarcinoma of the cecum, grade 4, measuring 9 by 7 by 4 cm.

This patient returned to the clinic on Feb 18, 1938 and stated that he had passed four or five loose stools daily and had had rectal burning for five months. Previous to the onset of these symptoms he had been entirely well. There had been some rectal bleeding, less during the two months preceding admission.

Examination revealed an annular lesion beginning at the dentate margin. The pathologic report on the resected specimen was annular, ulcerating adenocarcinoma, grade 2, measuring 5 by 5 by 2 cm. Just lateral to the growth was a pedunculated adenocarcinoma, grade 1, measuring 2 by 2 by 1 cm. The lymph nodes were not involved.

CASE 20—A man aged 49 years came to the clinic on Aug 26, 1935. Two years before his admission, there had been diarrhea for one month. For one year prior to admission to the clinic, there had been gnawing pain in the abdomen associated with the return of diarrhea, which was persistent and progressive. For five or six weeks before admission, each day he had passed eight to ten mushy stools free of blood. During this interval there had been a loss of 10 pounds (4.5 Kg).

Examination revealed a lesion in the region of the rectosigmoid, and at the time of surgical exploration a large mass also was discovered in the cecum. The pathologic report on the resected specimens was adenocarcinoma of the cecum, grade 3, measuring 7 by 8 by 3 cm, without involvement of lymph nodes, and also ulcerated, pedunculated adenocarcinoma of the sigmoid flexure, grade 3, measuring 6 by 4 cm.

The patient returned on Nov 17, 1937, he stated that he had been well for one year, and then had become aware of a heavy feeling in the lower part of the abdomen and had required liquid petrolatum to insure bowel movements. Examination revealed a lesion in the descending colon. The pathologic report on the resected specimen was mucoid adenocarcinoma of the descending colon, grade 3, measuring 8 by 5 by 2 cm, with extension to the serosa. The lymph nodes were not involved.

CASE 21—A man aged 55 years came to the clinic on Nov 29, 1933, he related a history of progressive weakness and loss of weight during the preceding three months. During the six weeks prior to his admission, there had been pain and tenderness in the right lower abdominal quadrant, as well as some generalized abdominal cramps and gradually increasing constipation. During the past year the

patient had been aware of a mass in the right lower abdominal quadrant. Examination revealed a lesion in the ascending colon. The pathologic report on the resected specimen was ulcerating, colloid adenocarcinoma of the ascending colon, grade 2, measuring 12 by 7 by 3 cm, with peritoneal involvement.

The patient returned on July 19, 1938, he stated that he had been well until one year prior to his second admission. Then constipation had developed, aching pains in the rectum and testes had occurred, mostly at night. Each day he had passed four to ten mushy stools, which were often bloody, and occasionally he had been awakened three to four times at night with the desire to defecate. Bleeding had been more severe in the three months preceding admission.

Examination revealed a huge, fixed, inoperable lesion in the lower part of the rectum. The pathologic report was colloid adenocarcinoma, grade 1.

CASE 22—A man aged 40 years came to the clinic on April 14, 1926, he related a history of easy fatigue, increasing constipation and daily use of laxatives for two years preceding admission. Examination revealed a lesion in the cecum. The pathologic report on the excised specimen was colloid adenocarcinoma, grade 1, measuring 8 by 2 by 2 cm.

The patient returned in May 1927 and appeared to be in good health. He returned again on June 6, 1936, at which time he complained of abdominal cramps and two to six loose stools daily for one year. There had been no bleeding.

Examination revealed a lesion in the descending colon as well as a small sessile polyp in the rectum. The pathologic report on the resected specimen was adenocarcinoma of the descending colon, grade 2, without involvement of lymph nodes.

CASE 23—A woman aged 62 years came to the clinic on June 10, 1931. She had been perfectly well until six months before her arrival at the clinic. Then there developed tenesmus and rectal urgency, together with the passage of gas and blood. She had become increasingly constipated. Examination revealed a lesion in the lower third of the rectum. The pathologic report on the resected specimen was adenocarcinoma of the posterior rectal wall, grade 3, measuring 4 by 6 by 6 cm. The lymph nodes were not involved.

The patient returned to the clinic on July 2, 1934, she related a history of increasing cramps in the midabdomen, aggravated by meals. The previously performed colostomy was functioning well. Roentgenologic examination revealed a filling defect in the cecum. The pathologic report on the resected specimen was annular ulcerating papillary adenocarcinoma of the cecum, grade 3, measuring 9 by 7 by 7 cm, with multiple small polyps and diverticula proximal and distal to the growth. The lymph nodes were not involved.

COMMENT

In some of the cases cited, such as case 6, the possibility of implantation might be thought of, but in this case and in other similar cases, careful pathologic study failed to reveal any connection in the wall or lining of the bowel between the distal and the proximal growth. Both arose at points distant from one another in the rectal mucosa.

A critical analysis of some cases, such as cases 12 and 13, might raise the question. Why is not one of the lesions an extension from the other? However, even if involvement of lymph nodes was found,

evidence of any connection between the two lesions could not be ascertained. They were individual lesions arising in close proximity from different sites in the mucosa of the bowel.

It is probably a fact that in many instances multiple independent lesions in the bowel are not recognized. The importance to the patient of the physician's failure to exclude the possibility of other lesions is apparent. It is interesting to speculate on the proportion of poor results after operation for cancer that are attributable to synchronous or metachronous lesions, unsuspected and therefore undiscovered. Curability by operative means will improve, therefore, only as diagnoses are made earlier and are thorough. That is a responsibility of the clinician, and it is a great one indeed. When a diagnosis of hemorrhoids is made only after all other possible causes of bleeding from the bowel have been excluded, when digital and proctoscopic examinations of the rectum and the sigmoid flexure become routine procedures, the percentage of cases of cancer of the large bowel in which the condition is inoperable when first seen by the surgeon will diminish.

Brindley,⁹ in a recent consideration of this subject, concluded that a patient with cancer is more likely to have a second malignant lesion develop than the subject who is free of cancer. The implication is clear. Once a patient has become the victim of a malignant lesion in the large intestine, he should be instructed adequately to watch for warning signs of recurring trouble. According to our experience many patients after having had a cancer of the colon removed tend to assume erroneously that they are from that time forth immune to a similar morbid process.

That the explanation of the pathogenesis of polyps may explain also the origin of cancer of the colon seems more than likely. Robertson put it nicely when he said "The usual growth of cells is so well regulated that parasitic masses do not occur. Cancer, then, does not come from 'stimulation of growth' as is so frequently asserted but because the normal mechanism for governing orderly growth is disturbed." That there must be a force which governs normal growth becomes almost apparent when one observes the fineness of adjustment in the healing of wounds. The repair of injured tissue progresses at a rapid rate, but as needed repair approaches completion the rate of proliferation of tissue becomes slowed and finally is reestablished at the normal rate. Proliferation is an inherent characteristic of all tissues. Whether the cancers reported in this paper originated in polyps remains unproved. That polyps play a role in the genesis of some cancers cannot be denied. These facts emphasize the importance of a careful examination of the entire large intestine when cancer is found at any point in it.

⁹ Brindley, G. V. Multiple Primary Malignancies of the Large Intestine, *South M J* **31** 355-362 (April) 1938.

Progress in Internal Medicine

REVIEW OF NEUROPSYCHIATRY FOR 1940

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BOSTON

Several important books have appeared this year in the field of neurology and psychiatry. In the first place stands Wilson's "Neurology,"¹ published posthumously and edited by Wilson's great friend Nimian Bruce. The book is complete, scholarly and well written. It supplants the old Oppenheim, and to say that is high praise indeed. As a book of reference it is indispensable, but it is not a handbook for students.

Another important book by an English author is the "Selected Writings of Sir Charles Sherrington," edited by Denny-Brown.² The published papers of Sir Charles are scattered through so many journals and over such a long period of time that many of them are difficult to find. They contain a mass of systematic observation and faithful record that gives a classic example of the scientific method and makes a monumental contribution to the literature of the nervous system. It is therefore a great boon to any neurologic library to have this book of sources with well chosen reprints and abstracts, which include such important observations as the original description of the spinal and of the decerebrate animal, the experimental isolation of skin and muscle segmentation, the proof for muscle sensibility, the motor representation in the primate cortex and the fundamental work on reciprocal innervation and postural reflexes. Any one of these contributions is enough to have made a physiologist great.

A different production in every way is "The Varieties of Human Physique," by Sheldon and his co-workers.³ Here is the work of a trained specialist bringing to medicine the results of labors in anthropology and mathematics. Many earlier workers had classified persons into types, from Hippocrates, who divided mankind into the *habitus*

1 Wilson, S. A. K. "Neurology," Baltimore, Williams & Wilkins Company, 1940.

2 Denny-Brown, D. "Selected Writings of Sir Charles Sherrington," New York, Paul B. Hoeber, Inc., 1940.

3 Sheldon, W. H., Stevens, S. S., and Tucker, W. B. "The Varieties of Human Physique," New York, Harper & Bros., 1940.

apoplectic and the *habitus phthisicus*, through Walker, in 1852, with his "nutritive beauty" (Venus), "locomotive beauty" (Diana) and "mental beauty" (Mineiva), to Kretschmer, in 1925, with his widely accepted "pyknic, athletic and asthenic" types. All had more or less definite ideas that these body types corresponded to mental traits. Sheldon and his associates have taken three aspects of bodily constitution, which they selected after many preliminary observations. These the authors call "endomorph," "mesomorph" and "ectomorph." Illustrations show the types better than any words, but, briefly put, endomorph can be described as the dominant component in the soft, round people with big viscera, mesomorph means a predominance of muscle and bone and ectomorph describes the lean, fragile, type with relatively large skin area and brain. The analogy with the three embryonic layers is obvious. In his psychiatric work Sheldon photographed about 3,000 young schizophrenic and about 300 manic-depressive patients. The hebephrenic and catatonic patients are highly ectomorphic as a group. The manic-depressive patients seem to be more mesomorphic than endomorphic. Paranoid types resemble these more than they resemble the catatonic or hebephrenic type. The book is interestingly written and well illustrated. Taken with the recent studies on the inheritance of schizophrenia and manic-depressive psychosis,⁴ it makes the superficial classification of these as "functional psychoses" more indefensible than ever.

In "Mental Health,"⁵ a volume of contributions by many speakers at the Christmas meeting 1938 of the American Association for the Advancement of Science, there is presented a great array of disconnected facts concerning mental disorders. The discussions at the end of each group of papers are carefully prepared and bring together the diverse data into coherent expositions. For instance, summarizing papers on genetics, syphilis, alcohol, vitamins and fatigue are correlated and discussed in an able chapter by Myerson. Other sections are on methods of research, environment, administration and education. The papers and their bibliographic references make the volume a most useful book for reference.

Brain has brought out a fourth edition of his series, "Recent Advances in Neurology."⁶ It is written in clear style and is not marred by too

4 Kallman, F. J., and Rypins, S. J. *Genetics of Schizophrenia*, New York, J. J. Augustin, 1938.

5 Moulton, F. R., and Komora, P. O. *Mental Health*, Publication 9, American Association for the Advancement of Science, New York, Science Press, 1939, p. 470.

6 Brain, R. W. *Recent Advances in Neurology*, ed. 4, Philadelphia, P. Blakiston's Son & Co., 1940.

much abstracting and quotation, references are well chosen and plentiful. Of especial interest to internists are the chapters on headaches, sleep, the hypothalamus, micturition, viruses, deficiency disorders, disorders of muscle and meningitis.

HEADACHE

Brian's review of headache gives the background of experimentation in England by Pickering,⁷ Northfield and others. In this country Wolff and his co-workers⁸ have contributed important studies. They have shown that stretched cranial arteries give rise to certain headaches and that the large arteries at the base of the brain are responsible for the headache which follows intravenous injection of histamine. Extracerebral arteries make only a minor contribution to histamine headache,⁹ but the headaches of migraine and hypertension are caused largely by dilatation of arteries in the scalp and dura. Penfield and McNaughton¹⁰ believe that many headaches are caused by stretching the dura and dural sinuses. If diagnostic nerve block relieves the pain, radical neurectomy, or even operation on the dural lesion, will often cure the headache. The ophthalmic branch of the trigeminal nerve is the nerve most frequently involved. Wolff showed, furthermore, that the headache of migraine and that associated with hypertension were not relieved by increasing intracranial pressure, whereas histamine headache is reduced by increasing intracranial pressure. This is further evidence that the former kinds of headache are related to stretching of the arteries of the scalp. By observations on a particularly well trained patient they proved that the scotomas which come as prodromal warnings of a migraine attack are due to cerebral vasoconstriction. Thus the essentials of a migraine attack are cranial vasoconstriction followed by vasodilatation, but in the first case symptoms come from within the brain and in the second from the scalp and perhaps the dura. Treatment with amyl nitrite will relieve the first, while ligation of the appropriate branches of the common carotid artery will relieve the second.

7 Pickering, G. W. *Brit. M. J.* **1**: 907, 1939.

8 Wolff, H. G., Cahan, A. M., and Schumacher, G. A. Read at the Sixty-Sixth Annual Meeting of the American Neurological Association, Rye, N. Y., June 6, 1940. Sutherland, A. M., and Wolff, H. G. Experimental Studies on Headache. Further Analysis of the Mechanism of Headache in Migraine, Hypertension and Fever, *Arch. Neurol. & Psychiat.* **44**: 929 (Nov.) 1940.

9 Ray, B. S., and Wolff, H. G. Experimental Studies on Headache. Pain-Sensitive Structures of the Head and Their Significance in Headache, *Arch. Surg.* **41**: 813 (Oct.) 1940.

10 Penfield, W., and McNaughton, F. Dural Headache and Innervation of the Dura Mater, *Arch. Neurol. & Psychiat.* **44**: 43 (July) 1940.

DEVELOPMENTS IN PSYCHIATRY

Since my review of the insulin treatment of schizophrenia in 1937,¹¹ the tide of enthusiasm rose to a flood amounting to thousands of shock treatments in various hospitals and now has ebbed, leaving much incidental knowledge that will eventually advance psychiatry. It is now demonstrated beyond reasonable doubt that repeated insulin shock destroys nerve cells in the brain.¹² It is probable that the mechanism is asphyxial, resulting from hypoglycemia. Meduna's convulsive therapy closely followed the insulin shock treatment, and is being even more widely used because the technic is simpler and less time consuming. Fits have even been given to patients in office practice.¹ The treatment was originally designed to be used in cases of schizophrenia, this was because Meduna believed there was a "biologic antagonism" between epilepsy and schizophrenia—a thesis which is based on no good evidence. Recently, however, it has been used for manic-depressive psychosis and neurosis and was even recommended by Meduna for epilepsy.¹³ Finley and Brenner¹² and others have shown that metrazol, like insulin, causes small islands of nerve cell destruction in the brain. The whole subject has been carefully and critically reviewed in three papers by Katzenelbogen.¹⁴ He concludes by saying

The therapeutic achievements in schizophrenia have of late suffered a serious set-back, according to reports from many quarters. The loss in this field has been, however, amply compensated by the very favorable therapeutic results obtained in varied places in affective psychoses, and psychoneuroses. Emphasis is placed, as would be expected, mainly on shortening the duration of these disorders. While there appears to be justification for using convulsive therapy—which is not entirely devoid of danger to life and certainly of serious complications—in the last-mentioned conditions only if they are conspicuous by both severity and perseverance, it is to be regretted that this very diastolic procedure is becoming routine practice. Instead of being reserved for special particularly ominous conditions, it is being used rather indiscriminately, without due regard for the nature and seriousness of the illness, and without the circumspection such a procedure should command. For my part, I cannot help deploring the fact that the indiscriminate, universal use of "shock" and other supposedly short-cut therapies tends undeservedly to reduce the present-day treatment in psychiatry, to a level which turns the clock back to the Benjamin Rush epoch of the 18th century.

11 Cobb, S. Review of Neuropsychiatry for 1937, *Arch Int Med* **60** 1098 (Dec) 1937.

12 Finley, K. H., and Brenner, C. Read at the Sixty-Sixth Annual Meeting of the American Neurological Association, Rye, N. Y., June 6, 1940.

13 von Meduna, L. Read at the Ninety-Fifth Annual Meeting of the American Psychiatric Association, Chicago, May 8, 1939, *Rev neurol e psychiat de São Paulo* **5** 101, 1939.

14 Katzenelbogen, S. *Psychiatry* **2** 493, 1939, **3** 211 and 409 1940.

I heartily endorse this opinion and merely add that to my mind only if the situation of the patient is hopeless enough to justify cerebral destruction for alleviation of symptoms does the treatment seem reasonable. To employ such drastic measures in treatment of recoverable mental disturbances such as ordinary depression or neurosis, is unwarranted.

The new methods of shock therapy have had another result. They have awakened the medical enthusiasm of many psychiatrists who had been distrustfully watching the therapeutic pendulum swinging toward the side of the dynamic psychologists, who believe that all neuroses and at least some aspects of psychoses are explainable on the basis of disorganized interpersonal relations. Thus, insulin, metrazol, nitrogen asphyxia and electric shock were sometimes taken up, not with an enquiring scientific spirit, but with a desire to show the physicians of the psychologic school that mental ills were basically "organic."¹⁵ The result is that the two camps in psychiatry, which were beginning to get together as physiologists and psychologists, are now tending to split apart again. This is a situation to be deplored, it leads to schism in the medical profession, intolerance and formation of new special societies. In contrast to the psychiatrists who treat neurosis with metrazol shock, take, for example, the position of Harry Stack Sullivan. In his William Alanson White lectures¹⁶ Sullivan describes hysteria in a vivid manner.

Hysteria the mental disorder to which the self-absorbed are peculiarly liable, is the distortion of interpersonal relations which results from extensive amnesias.

In people who show our self-absorbed type of performances, however, the element of representative fantasy continues as a major ingredient of life. All sorts of interpersonal prehensions are fogged into what is called "wishful" distortions or misinformation about people. These people have no grey, everything tends to be black or white. Their friends are simply wonderful people. People whom they dislike are just simply impossible. Their "love" is melodramatic to a degree that confounds its object—excepting the object be another self-absorbed person. Together, by a sustained miracle of accommodating—or ignoring—the individualistic misconceptions of each other, two of these folk can have quite a good time. With the rest of us, however, they are apt to be disappointed, wounded, misunderstood. And we, if we care to study the processes at work, cannot but marvel at the failure of learning which has left their capacity for fantastic, self-centered, illusion so utterly unaffected by a life-long series of educative events. These people integrate situations with foggy embodiments projected upon us from their fantasies about themselves.

Such descriptions are too "true to life" (i.e., they agree with one's personal experience too well) to be ignored as not "scientific." One

15 For a discussion of the uselessness of the distinction between "organic" and "functional" conditions see my review of neuropsychiatry for last year (Arch Int Med 64 1333 [Dec.] 1939)

16 Sullivan, H. S. Psychiatry 3 1, 1940

must accept the fact that observations made on the "higher functional activities of man," as Pavlov called psychologic reactions, can be controlled only in a limited way, just because of their complexity. The human organism is a very highly integrated unit, it acts as a unit as long as it is in normal health. It is only in disease, maladjustment or impossible environment that disintegration interferes with this normally smooth mechanism. Moreover, the breaking down of the unit into separate departments has no biologic basis, but is only the attempt of different academic departments to define their limits in the great field of biology. Psychologic phenomena are obviously the most complex of all functions of the body, but by this I am only stating that they are part of the physiology, although the most highly integrated part. In order to practice psychiatry one should insist on a training that gives to the physician both an understanding of human nature, as suggested in the quotation from Sullivan, and an understanding of the physiology of the brain and other organs. The need is for well balanced men trained in medicine, neurology and psychiatry.

The death of Austen Fox Riggs, on March 5, 1940, is a great loss to American psychiatry, for he was one of the pioneers in modern psychotherapy and throughout his life followed a sound middle course in his attitude toward mental ill and in his treatment of psychoneurotic patients. As far back as 1908 he stated emphatically ¹⁷

The concept of psychophysiological unity is the basis of enlightened monistic philosophy and is the only concept which agrees with and is supported by the laws of nature.

He held to this belief that "psychology is only a sort of inclusive physiology" ¹⁸ throughout the thirty years of his neuropsychiatric practice. Many have since waged this war to uphold the unity of the human organism, but few have so steadily stuck to their guns and proved their points by successfully putting them into practice. He looked on suggestion as a biologic phenomenon that must be recognized and skilfully used by the physician, almost always indirectly, with avoidance of such crude technics as exhortation and hypnosis. He pointed out how frequently physicians undermined their good medical work through the adverse suggestion given to the patient by anxious or hurried manners and thoughtless words. Education was the mainstay of treatment, it was planned to give to the patient "knowledge of his difficulty, of his own assets and liabilities, and finally to teach him how to adjust himself to these difficulties" ¹⁹. As early as 1912 he taught that the person was made up of four levels anatomically and behavioristically—the reflex, the

17 Riggs, A. F. *M. Rec.* **73** 1071, 1908.

18 Riggs, A. F. *Ment. Hyg.* **6** 263, 1922.

19 Riggs, A. F. *Boston M. & S. J.* **189** 269, 1923.

instinctive, the intelligent and the ethical²⁰ He explained "nervousness" as arising on the basis of conflict between these levels, and he was fully aware of the effects of amnesia and how to get around this by letting the patient talk His views were not widely known because he wrote little, but he taught many pupils and sent them out to practice and teach Although he is gone, his work will go on through the Austen Riggs Foundation at Stockbridge, Mass., organized through the beneficence of his many devoted patients and carried on by the men he trained

FUNCTION OF THE FRONTAL AREAS OF THE HUMAN BRAIN

The case of the "crow-bar skull" preserved in the Warren Museum at the Harvard Medical School, is the first instance reported²¹ of an injury to the frontal areas of the brain that seemed to cause marked personality changes The patient was an energetic and efficient foreman of road builders On Sept. 18, 1848 he was tamping a blast into a drill in a rock when the powder exploded and drove the tamping iron through the left frontal bone and orbit, into the left frontal pole of the brain and out through the vault of the skull a little to the right of the midline He recovered miraculously but became "irreverent, profane and impatient of restraint" and was unable to hold a job He died thirteen years later of epilepsy Since then much experimental and clinical work has been done to elucidate the function of the frontal areas of the brain and to locate the seat of human "intelligence" Some of the animal work clearly forecast the results now found in the human subject For example, Bianchi,²² in 1893, after frontal ablations on monkeys, said that the animals no longer showed any restraint or resourcefulness in small difficulties and that "utilization of past experience was absolutely wanting" Shepherd,²³ in 1907, found that cats and monkeys lost recent memory, i. e., their training in opening a food box Recently Fulton and his colleagues have done remarkable work on functional localization in the brains of the higher apes,²⁴ work which apparently led directly to operations on human patients, for Egas Moniz²⁵ mentioned the observation of Jacobsen²⁶ in Fulton's laboratory that a chimpanzee deprived

20 Riggs, A. F. *Talks to Patients*, Stockbridge, Mass., 1912, p. 37, also in Coon, G. P., and Raymond, A. F. *A Review of the Psychoneuroses at Stockbridge 1940*, Brattleboro, Vt., Hildreth & Co., 1940

21 Harlow, J. M. *Publ. Massachusetts M. Soc.* **2**: 329, 1868

22 Bianchi, L. *Mechanism of the Brain and the Function of the Frontal Lobes*, Edinburgh, E. & S. Livingstone, 1922

23 Shepherd, I. *The Frontal Lobes*, 1907, cited by Bianchi²²

24 Fulton, J. F. *Physiology of the Nervous System*, London, Oxford University Press, 1938

25 Egas Moniz. *Tentatives opératoires dans le traitement de certaines psychoses*, Paris, Masson & Cie, 1936

26 Jacobsen, C. F. *A Research Nerv. & Ment. Dis.*, *Proc.* (1932) **13**: 225, 1934

of her frontal areas, although less able to perform complex tasks, lost her anxiety over failure and seemed much more placid

It was not only this experimental work which led to the present operation of "lobotomy" for agitated mental states, but the psychologic observation on certain cases in which operations for tumor had caused bilateral damage to the frontal areas of the cerebrum. Before describing these cases it is important to define just what is meant by the anatomic term "frontal area." The division of the brain into "lobes" is ineffect and outmoded—frontal, parietal, occipital and temporal lobes are arbitrary morphologic divisions, with little biologic significance. It is now known that many areas of the cortex are recognizable by physiologic and histologic criteria that show the old division into "lobes" to be meaningless.

The "frontal" lobe is usually defined as all of that cortex and white matter lying in front of the central fissure of Rolando (figs 1 and 2). This, then, includes the motor areas 4, 6 and 8, with the motor-speech area, 44, the frontal associative fields, 9, 10 and 11, and the triangular area, 45 with area 46 above it and area 47 below. On the mesial aspect of the hemisphere area 32, lying between the mesial parts of areas 11 and 8, should be included. These anterior zones (9, 10, 11, 32, 45, 46 and 47) constitute the "frontal areas,"²⁶ and the terms "frontal lobectomy" and "frontal lobotomy" are usually used as meaning removal or undercutting of areas 9, 10, 11 and sometimes 32, 45, 46 and 47. The term "prefrontal lobe" seems to me illogical, in fact linguistically ridiculous, since an area cannot be in front of the front and since no anatomic fissure separates these areas off into anything like a lobe.

Starting with this definition, the question is: What is really known of the normal function of the frontal areas in man? Scientifically speaking, the answer must be "Very little," because no case is known in which a normal man has been examined and then deprived of these areas and reexamined. Hebb and Penfield²⁷ say that it may be that no laboratory study will be adequate to reveal the defects that follow frontal injury because of the difficulty of obtaining good premonitory rating of ability. One must rely on observations concerning, first, brains already deformed and partially destroyed by tumors and, second, patients with epilepsy or mental symptoms who undergo cerebral operation for the relief of their symptoms. Obviously in neither case can satisfactory examinations be made before operation, so no scientific controls exist. The best one can do is to examine the cases and amass such data as are available. Harlow's case of the "crow-bar skull" has already been cited, but this is of more historical than neurologic interest, because the

²⁷ Hebb, D. O., and Penfield, W. Human Behavior After Extensive Bilateral Removal from the Frontal Lobes, *Arch Neurol & Psychiat* **44**: 421 (Aug) 1940.

exact injury to the brain is not known, it had to be reconstructed from the skull specimen (fig 1). The same can be said of a great deal of literature on the effects of frontal injuries in the last war. The data are interesting but not convincing. There is an extensive literature on unilateral lesions of the frontal areas. The more careful observers have been able to detect slight changes in personality (Penfield and Evans²⁸), loss of initiative (Foerster²⁹), loss of the power of abstraction (Goldstein³⁰) and incapacity to resolve situations (Feuchtwanger³¹). Some authors, such as Grünthal,³² have even expressed the belief that they can localize symptoms, for example, emotional distur-

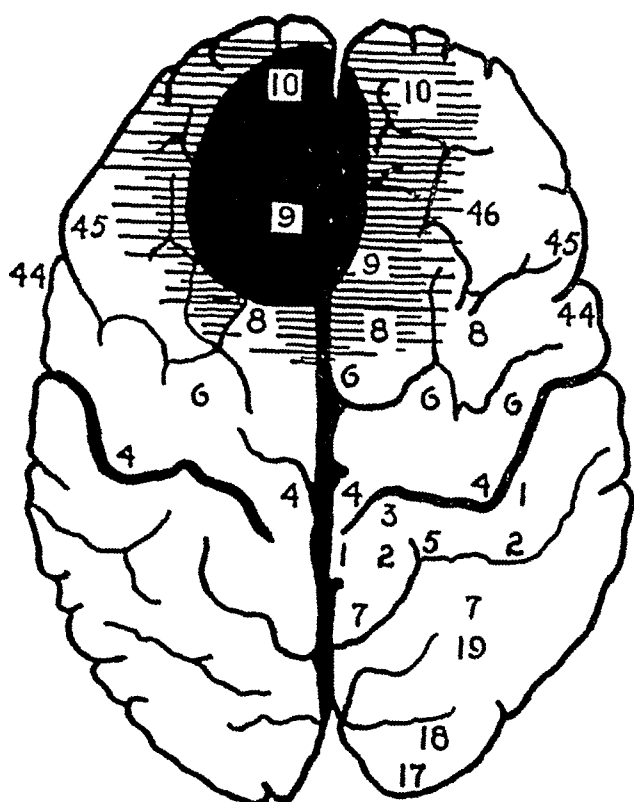


Fig 1—"The crow-bait" case from the Warren Museum at Harvard University (Harlow²¹). Reconstructed from the skull.

bances are likely to follow lesions of the orbital surface of the frontal lobe (area 11), whereas intellectual deterioration results from injury to the lateral convex surface (area 10). Nevertheless, after reading the reports of these numerous and extensive unilateral injuries, one is most impressed by the lack of symptoms.

28 Penfield, W., and Evans, J. *Brain* **58** 115, 1935.

29 Foerster, O. *Ztschr f d ges Neurol u Psychiat* 1918, cited by Rylander.³³

30 Goldstein, K. *J Neurol & Psychopath* **17** 27, 1936.

31 Feuchtwanger, E. *Die Funktionen des Stirnhirns*, Berlin, Julius Springer, 1923.

32 Grünthal, J. *Ztschr f d ges Neurol u Psychiat* **129** 350, 1930.

Rylander,³³ of Stockholm, has given the results of the most recent and carefully controlled work in his monograph. It is superior to most of the previous work because careful psychologic tests were carried out in cases in which there were known operative lesions. He gives thorough reports of 32 cases in which part of one frontal lobe was removed for tumor or (in a few cases) for abscess, usually about two thirds of the lobe was removed, i. e., areas 8, 9, 10, 11 and 45, but in some instances the excision was smaller. Careful study of the case records, however, reveals that 16 of the patients probably had bilateral injury and 14 of these showed marked mental change. His follow-up examinations showed that in 25 cases there was "diminished inhibition of affective response" and in 20 distinct euphoria, in 14 cases restlessness was present and in 12 loss of initiative. Intellectual faculties were disturbed in 21 instances. These intellectual changes he specifies as loss of attention, in 10 cases, slow thinking and lack of ability to "keep up," in 14, loss of memory for details, in 21, weak association, in 20, and poor memorization tests, in 11. Six patients showed a marked increase in appetite and weight with marked personality change. Rylander concludes:

Mental changes occur after excision of parts of the frontal lobes. These changes are exhibited in alteration of personality. Generally they are not of such degree as to destroy the subject's ability to lead a normal social existence, but they can be fatal to persons doing qualified intellectual work.

Four cases have been reported in which both frontal areas were excised in order to remove a large tumor. The first and most carefully reported is Dandy's case, he operated on the man in 1930, and after prolonged and careful study Brickner published the psychologic observations in 1936. A reconstruction of the area removed from the left hemisphere is shown in figure 2 (black), from the right hemisphere a slightly larger excision was made, including probably a little more of area 8 and area 44. The results on the patient's mentality are given at length in Brickner's book³⁴, briefly, the patient showed (1) limitation of the capacity to associate and synthesize, e. g., distractibility with impairment of selection, retention and learning, (2) impairment of restraint of emotion with boasting, anger and hostility, (3) additional symptoms, such as impairment of abstraction, judgment and initiative with euphoria and increased slowness, stereotypy and compulsiveness.

33 Rylander, G. *Personality Changes After Operations on the Frontal Lobes*, London, Oxford University Press, 1939.

34 Brickner, R. M. *Intellectual Functions of the Frontal Lobes*, New York, The Macmillan Company, 1936.

Ackerly³⁵ reported a similar case in which an operation was performed in 1933 by Spurling. The left frontal area, however, though greatly compressed, was not actually removed. The symptoms were more like those reported by Rylander than by Brickner, but all have points of similarity. Euphoria was marked, and the patient said of the surgeon "He cut out my worry!" The patient reported on by Karnosh³⁶ in 1935 showed emotional instability and distractibility. The patient in David and Askenasy's³⁷ case is interesting because she remarked after recovery, "I understand things better now, but they don't stir me up."

The most striking results, however, have come from the surgeons who have been performing "lobectomies" and "lobotomies" on psychotic patients for the relief of mental symptoms. As in the cases of tumor,

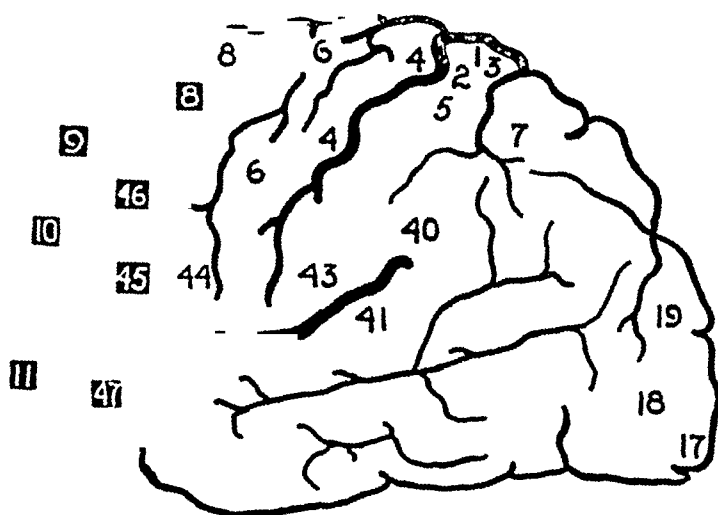


Fig 2—The left cerebral hemisphere in the Dandy and Brickner case, reconstructed from Brickner³⁴. The amount of frontal lobe probably removed is shown in black.

one must admit that the evidence as to the normal function of the frontal areas is not convincing, because all the patients were psychotic before operation and there could be no normal controls. Moreover, as Hebb and Penfield²⁷ point out, disconnected and perhaps asphyxiated tissue is left in the brain after lobotomy, and this pathologic tissue may cause symptoms. Nevertheless, the mass of data accumulating is impressive and points in the direction already indicated by the cases of tumor previously cited. Egas Moniz started this form of treatment in Portugal, publishing his first results in 1936, since then he has done many more

35 Ackerly, S. *Am J Psychiat* **92** 717, 1935

36 Karnosh, L. J. *J Indiana M A* **28** 567, 1935

37 David, M., and Askenasy, H. *Encéphale* **1** 34, 1939

operations in various types of cases,³⁸ but the reports are so meager that one cannot judge of the work. In an earlier paper³⁹ he stated that the best results are with patients suffering from agitated depression. Of 20 cases, he produced cure in 7, amelioration in 7 and no effect in 6. Only 1 of the 20 cases, however, is given in enough detail to allow the reader to judge for himself as to the diagnosis and result.

In this country Freeman and Watts⁴⁰ and Lysterly⁴¹ have taken up the work and a few such operations have been done by other surgeons, notably Mixer,⁴² who reported 2 cases of lobotomy with careful psychiatric examination and who in 1936⁴³ performed a bilateral "frontal lobectomy" on a boy for epilepsy and noticed afterward that the patient lost his irritability and hostile attitude and became much easier to handle at home. Hebb and Penfield²⁷ have made the most recent and one of the best reports of a case of bilateral frontal lobectomy in a young man who was injured at the age of 16, was epileptic for ten years and was operated on at the age of 27. The studies are thorough from the points of view of psychology and anatomy. Their emphasis, however, is on the significance of the great improvement following the removal of abnormal frontal poles and the great diminution of abnormal electrical activity. The areas mutilated by the trauma were approximately 8, 9, 10 and 11 while the surgical procedure probably removed normal parts of areas 6, 8, 25, 32, 33, 46 and 47. The patient changed from an irresponsible, stubborn, restless and forgetful epileptic person to one with a "pleasant personality," who was "considerate of other patients" and had had only two seizures in fifteen months. The case demonstrates clearly the detrimental effect of the presence of pathologic lesions in the brain. The authors conclude from their psychologic examinations that removing a third of both frontal lobes need not cause gross deterioration. I believe, however, that the only cases that can be of much help in this problem are those of adult persons with personality traits well known before the trauma or disease.

38 Egas Moniz. *Am J Psychiat* **93** 1379, 1937, footnote 25.

39 Egas Moniz. *Encephale* **31** 1, 1936.

40 Freeman, W., and Watts, J. W. *South M J* **30** 23, 1937, *M Ann District of Columbia* **6** 267, 1937, *Yale J Biol & Med* **11** 527, 1939. Freeman, W. Read before the International Neurological Congress, Copenhagen, August 1939.

41 Lysterly, J. G. *South Surgeon* **8** 426, 1939, *J Florida M A* **25** 225, 1938.

42 Mixer, W. J., Tillotson, K. J., and Wies, D. D. Frontal Lobotomy in Two Patients with Agitated Depression. Therapeutic Evaluation and Further Reference to Function of the Frontal Lobes, *Arch Neurol & Psychiat* **44** 236 (July) 1940.

43 Mixer, W. J. Personal observation.

From the published papers it would seem that Freeman, Watts and Lyeily have done in all about 100 "prefrontal lobotomies" ⁴⁴ The results of their work are summarized in the papers already referred to This summarizing is the weakness of the work, only one adequate case report is given Nevertheless, the results are interesting The main symptoms relieved by the operation have been depression (80 per cent of 49 cases), agitation (70 per cent of 51 cases), compulsion (70 per cent of 27 cases), suspiciousness (55 per cent of 17 cases) and irritability (33 per cent of 14 cases) Symptoms produced have been inertia ("emotional flattening" or laziness), in most cases, hypomania (euphoria, playfulness and poor judgment), in about half the cases, and marked gain in weight in 40 per cent Freeman and Watts divide their results into two classes The primary results consist of inertia, lack of ambition, reduction in consecutive thinking loss of "self consciousness," indifference to the opinion of others and satisfaction with results of inferior quality The secondary results are euphoria, evasion, bluffing, talkativeness, aggressiveness, teasing, indecency in speech and act, inattention and poor judgment

From the physiologic standpoint these operations of Egas Moniz, Freeman, Watts and Lyeily are of great interest They indicate that in man bilateral loss of the frontal areas causes symptoms much like those postulated on the basis of animal experiments Moreover, these operations indicate that the symptoms observed in cases of tumor and trauma of the frontal areas of the brain are specific for frontal lesions and occur only when the lesions are bilateral

All observers agree that in cases of frontal lesions no especial quality of behavior is lost, it is rather as if there were a quantitative deficit This, taken with all the other data, leads to the conclusion that the frontal areas (as well as some parietal and temporal regions) are associative areas Stimuli reaching one or more of the receiving stations in the cortex (visual, auditory, tactile, etc.) spread rapidly through ever widening association paths to many areas of the cortex This is a process of "long circuiting" ²¹ of the nerve impulses, there is delay in response, time and opportunity are given to the cerebral organ to respond to an outside stimulus in the light of past experience I consider this the essential mechanism of intellect It cannot be localized narrowly because its full effectiveness depends on its widespread topography and multiplicity of pathways Lorente de Nó ⁴⁵ has given a hint as to this

44 I cannot accept the term "prefrontal," as previously explained, nor do I think that "lobotomy" describes this partial severing of the white tracts from the frontal areas It seems to me that "frontal leukotomy" would be a more descriptive name Worst of all is Freeman and Watts's title "psychosurgery"—suggesting that one operates on the symptoms Why not "vomitosurgery"?

45 Lorente de Nó, R J Neurophysiol 1 187 195 and 207, 1938

complexity and its capacity for continued, "reverberating" function. Destruction of these "association areas," it seems to me, would give just such symptoms as the surgeons and their co-workers have described. What is needed is more observation of these patients before and after operation by trained psychiatrists and psychologists, who will present the data fully in each case, as Rylander, Hebb and Penfield, and Brickner have done. The summaries of most of the other authors, although suggestive and interesting, are not convincing as scientific evidence.

From the standpoint of therapy, "lobotomy" of the brain to relieve mental symptoms calls for careful consideration. Is the surgeon justified in depriving a patient of the most important part of his intellect in order to relieve him of emotional troubles? In the results as interpreted by the surgeons themselves, it is seen that such an operation usually leaves the patient lazy and indiscriminating. In other words, one often takes away the highest integration ("conscience," or "superego" perhaps) in order to make the patient happier. In my opinion, this is a justifiable procedure only when the patient is old and the prognosis hopeless. Specifically, I can recommend the operation only in cases of prolonged agitated depression in persons over 60 years of age, or in rare instances in younger patients who show mental deterioration and neurologic and electroencephalographic evidence of cerebral degeneration. To perform such an operation on persons under 60 suffering from recoverable psychotic and neurotic states seems to me to be unjustified. Lastly, this "lobotomy" may well leave necrotic tissue and a scar that might later cause epilepsy. The procedure is so new that one has no evidence on this point, but such an outcome may be expected in a certain number of patients in from one to fifteen years.

News and Comment

Mississippi Valley Medical Society 1941 Essay Contest—A cash prize of \$100, a gold medal and a certificate of award are offered for the best unpublished essay on any subject of general medical interest, including medical economics, and of practical value to the general practitioner of medicine. Certificates of merit may also be granted to the physicians whose essays are rated second and third best. The winner will be invited to present his contribution before the next annual meeting of the Mississippi Valley Medical Society at Cedar Rapids, Iowa, Oct 1 to 3, 1941. Manuscripts should not exceed 5,000 words and should be type-written in English. Five copies should be submitted, and they should be in the hands of the secretary, Dr Harold Swanberg, W C U Building, Quincy, Ill, not later than May 1, 1941.

The following officers for the ensuing year were elected at the meeting held November 17. Dr E P Coleman, Canton, Ill, past chairman of the council of the Illinois State Medical Society, president, Dr Dan G Stine, Columbia, Mo, president-elect, and Dr Harold Swanberg, Quincy, Ill, secretary-treasurer.

The Sixty-Ninth Annual Meeting of the American Public Health Association—The meeting of the American Public Health Association and related organizations held in Detroit in October 1940 was the second largest in the history of the association.

The following officers were elected for the year 1940-1941: president, W S Leathers, M D, Nashville, Tenn, president-elect, John L Rice, M D, New York, treasurer, Louis I Dublin, Ph D, New York, chairman of executive board, Abel Wolman, Dr Eng, Baltimore, and executive secretary, Reginald M Atwater, M D, New York.

The following Committee on Public Health in the National Defense was appointed: W S Leathers, M D, chairman, Stanley H Osborn, M D, Huntington Williams, M D, and Abel Wolman, Dr Eng.

A resolution was passed emphasizing the necessity for maintaining civilian health as essential in national defense and pledging the united support of members to the national defense and to the maintenance of health in a free people.

The next annual meeting will be held in Atlantic City, N J, in October 1941.

Second Pan-American Congress of Endocrinology—The second Pan-American Congress of Endocrinology will be held in Rio de Janeiro, Brazil, March 5 to 8, 1941. The congress will include symposiums on a great variety of lectures by outstanding authorities in the field, by invitation.

Membership in the congress is requisite to participation in the scientific sessions or receiving publications. Physicians who are interested may obtain further details from the secretary, Dr Pedro A Barcia, Casilla de Correo 255, Montevideo, Uruguay.

CORRECTION

In the article by Dr Chester M Jones entitled "Gastroenterology: Review of Literature from July 1939 to July 1940," in the October issue (*ARCH INT MED* 66:893, 1940), the name "Corey" in the first line on page 936 and in footnote 107 should be "Carey."

Book Reviews

Hipertension arterial nefr6gena By Juan Carlos Fasciolo Pp 155 Buenos Aires Ferrari Hnos, 1939

This is a comprehensive study of the nature of the hypertension that occurs in dogs after the suitable application of Goldblatt clamps to the renal arteries. In the first chapter technics for the measurement of the blood pressure of a dog are discussed and the author's preference for the method of Loman and Dameshek is defended. Chapter 2 reviews briefly experimental methods for producing hypertension in dogs. The distinctive features of the type of hypertension provoked by renal ischemia, as described by other workers, are noted, and Fasciolo presents his own experiments to confirm them. These features may be briefly noted.

1 Unilateral partial occlusion of a renal artery causes (usually) a temporary hypertension.

2 Partial occlusion of both renal arteries causes a persistent and more severe hypertension, which may not be accompanied, at least early, by the retention of nitrogenous material in the blood.

3 The hypertension resulting from unilateral clamping is (a) augmented by removal of the normal kidney, or (b) cured by the removal of the ischemic one.

4 Partial occlusion of other visceral arteries does not provoke hypertension.

5 Unilateral or bilateral nephrectomy does not cause hypertension.

6 The elevation of blood pressure observed after the causing of renal ischemia is both systolic and diastolic.

With this background in mind Fasciolo examined the possible physiologic mechanisms for the production of this type of hypertension. Study of the literature satisfied him that the autonomic nervous system is neither responsible for the elevated blood pressure nor necessary for its production. He therefore performed experiments to determine the existence and nature of a humoral substance elaborated by the ischemic kidney and presumably destroyed by a normal one.

These experiments, in which he collaborated with Professor Houssay, are of the utmost interest. Earlier workers had attempted to find such a "humoral substance" by studying the action of various preparations of plasma or renal tissue extracts from hypertensive animals on certain test subjects. For reasons chiefly biologic the results of such studies have been equivocal from Tigerstedt's day to the present. The technic of Houssay and Fasciolo is biologically sound and relatively simple. The ischemic kidneys of dogs with hypertension were perfused by the carotid artery and jugular vein of a test dog. This animal was anesthetized with chloralose (chloral hydrate and dextrose), to preserve vasomotor reflexes, and was prepared for testing by having both kidneys removed. Chlorazol-fast pink was used as an anticoagulant, and the perfusion was carried out as expeditiously as possible. Many such perfusion experiments were performed. When the ischemic kidneys of dogs with hypertension were perfused, the blood pressure of the host rose promptly from 25 to 70 mm of mercury. Perfusion of normal kidneys rarely caused any alteration of the pressure of the host. One interesting experiment was performed on a kidney that had two renal arteries arising independently from the aorta, on one of which a Goldblatt clamp had been placed. The other kidney of this dog had been removed, and hypertension was present. The renal artery that had not been clamped was perfused first, and no variation of the blood pressure occurred. After twenty-five minutes the perfusion cannula was switched to the clamped artery and the ischemic zone of the kidney perfused.

Within six minutes the blood pressure of the host rose from 150 to 190 mm of mercury. In several experiments there was performed on one host successive perfusion by both kidneys of a dog in which hypertension had developed after the clamping of only one renal artery. In such experiments the normal kidney had no effect on the blood pressure, whereas the ischemic one caused a prompt elevation of the pressure of the host. This same type of experiment demonstrated conclusively that normal renal tissue was able to nullify the effect of the hypertensive substance. Similar experiments demonstrated that the adrenal glands, the pituitary and the thyroid gland and the gonads were neither necessary for the production of the hypertension nor able to prevent its development.

One chapter of the monograph reports Fasciolo's experience with the Luwen-Trendelenburg technic of perfusing the vascular system of a toad with citrated plasma of hypertensive dogs. Fasciolo reports that blood from the renal vein of an ischemic kidney caused an average diminution of 63 per cent in the flow of blood through this preparation. Blood from normal kidneys caused an average decline of 28 per cent. The remainder of the monograph dealing with histologic changes in the kidneys and retinas of hypertensive dogs is of less significance than the part just reviewed.

The monograph closes with a brief and sober chapter on the surgical treatment of hypertension. On the basis of the experiments discussed, one would anticipate no benefit from neurosurgical or endocrinologic operations for hypertension due to renal ischemia. In patients with such hypertension if renal disease is unilateral, nephrectomy is advisable, while for patients in whom it is bilateral, revascularization operations are suggested. The author admits that if hypertension is neurogenic he is unable to evaluate fairly the procedures suggested on the basis of his experiments.

Clinical Roentgenology of the Alimentary Tract By Jacob Buckstein, M.D., Visiting Roentgenologist (Alimentary Tract Division), Bellevue Hospital, New York, Consultant in Gastroenterology, Central Islip Hospital. Price, \$10.00, cloth. Pp. 652, with 525 illustrations. Philadelphia: W. B. Saunders Company, 1940.

This volume, by a roentgenologist with experience in roentgenology of the alimentary tract of twenty years at Bellevue Hospital in New York, is the latest contribution to gastroenterology and roentgenology. In general, the work is fairly complete and includes sufficient detailed description of functional and organic changes of the alimentary tract to serve as an approach to the best means of roentgenographic diagnosis in actual clinical practice. An effort has been made throughout to correlate etiologic and pathologic observations with the characteristic roentgen observations.

Attention has been devoted to the variations in the roentgen appearances of the normal organs of the gastrointestinal tract. Of value is the author's consideration of differential diagnosis relative to each clinical condition. Throughout the book points of importance are stressed by the use of italics. Brief reports and reproductions of roentgenograms of illustrative cases are included.

The book, consisting of fifty-eight chapters, is divided into eight main sections which cover the following subjects: esophagus, stomach, duodenum, small intestine, large intestine, herniation and eventration of the diaphragm, gallbladder and bile ducts, and, finally, spleen, liver and pancreas. The discussions of the value of the roentgen examination and the correlation of the pathologic changes with the roentgen appearance of the healing process in gastric and duodenal ulcers are timely. Of interest also is the author's consideration of chronic gastritis and duodenitis.

This book should serve as a valuable reference for any physician interested in the study of the alimentary tract. The text is clear and practical, and the illustrations are excellent. A fairly complete and indexed bibliography and a general index are included.

Brucellosis in Man and Animals By I Forest Huddleson, D V M, M S, Ph D, Research Professor in Bacteriology, Michigan State College, A V Hardy, M S, M D, Dr P H, Associate Professor of Epidemiology, Columbia University Medical School, J E Debono, M D, M R C P, Professor of Pharmacology and Therapeutics Royal University of Malta, Ward Giltner, D V M, M S, Dr P H, Dean of Veterinary Division and Professor of Bacteriology, Michigan State College Price, \$3 50 Pp 339, with 41 illustrations New York The Commonwealth Fund, 1939

The Commonwealth Fund has financed the publication of many excellent monographs Included among this splendid group is the book by Huddleson and his contributing authors on "Brucellosis in Man and Animals," a revision of the manual "Brucella Infections in Animals and Man," which came out in 1934 The revision is much larger and much more inclusive than the original volume The initial forty-five pages of the book have to do with the bacteriology of the genus *Brucella* This section is valuable to the laboratory worker and to the clinician, for it contains many excellent suggestions and much information concerning this interesting group of bacteria To the clinician the next hundred pages are of primary importance, for they give a thorough and complete presentation of the important features of the disease brucellosis After this is a section devoted to brucellosis in Malta, and then follows a section on treatment The last part of the book gives a considerable amount of laboratory data on man and cattle

Brucellosis in animals concerns the student of public health and the veterinarian From a recital of the divisions of the book it is obvious it was not written for the clinician alone, but also for others who have to do with the disease

The very complete bibliography, the excellent illustrations and the superb format of the book make it an outstanding example of the publishers' art Adverse criticisms of its contents would be few and far between One such criticism would be that it is doubtful that *Brucella melitensis* vaccine is as effective in the treatment of brucellosis as the authors have suggested On the whole, most clinicians have had unfavorable results and have judged the preparation to be of little value, however, their technic of administration of such vaccine may have been faulty

Verhandlung der Deutschen Gesellschaft für Kreislaufforschung Pp 424
Dresden and Leipzig Theodor Steinkopff, 1939

This is a report of the transactions of the twelfth annual meeting of the German Society for Study of the Circulation, which has 517 members Since there were thirty-three presentations at the aforementioned meeting, all of which are printed in this volume, it is obviously impossible to give more than a scanty review of the contents The chief subjects presented in this collection of individual articles are electrocardiography and cardiac failure There are twenty-one presentations on electrocardiography, including such diverse subjects as "A new cathode ray electrocardiograph," "Electrocardiography in gun shot wounds of the heart," "The conduction system in auricle and ventricle, particularly in horses" and "On the question of injury of heart muscle in diabetic coma"

There is a symposium on "therapy of heart failure" which includes presentations of the physiologic and of the pharmacologic aspects of heart failure, as well as an extensive article by Volhard on treatment Two guest lectures are printed, one on the "physiologic effects of extensive sympathectomy for essential hypertension" and one on "the circulation of the kidneys in experimental glomerulonephritis and the effects of denervation of them" There are additional presentations on such subjects as physiologic and pathologic changes in heart volume, and heart failure in diphtheria

This is essentially a book for the cardiologist, who should find much of interest in it One implication is that in Germany the study of the circulation is still essentially the study of the heart, for in this volume there is almost no consideration of the peripheral circulation

Diseases of the Gallbladder and Bile Ducts By Waltman Walters and Albert M. Snell Price, \$10 Pp 645, with 342 illustrations in 195 plates Philadelphia W B Saunders Company, 1940

This well printed and finely illustrated book, written by thorough experts, contains about all there is for the physician to know about diseases of the biliary tract. Beginning with the history of the subject and ending with the latest word on treatment, what is said, one feels throughout, is based on wide personal experience and is not mere "prattle without practice." The chapters on special topics by some of the other staff members of the Mayo Clinic, such as those on physiology by Bollman and on radiology by Kirklin, are also satisfactory.

Indeed the reviewer's only criticism is that in the effort to omit nothing the authors have indulged in a good deal of needless and confusing repetition. Chapter 4 (part II), for example, concerns "Chronic Cholecystic Disease," but later, in chapter 8, "Calculous and Non-Calculous Cholecystitis" is dealt with and the same material is to some extent gone over again. But neither of these chapters considers treatment, which is deferred to chapter 1 of part IV, again with some repetition. In brief, the reviewer believes that the book could have been done in much shorter space with corresponding reduction in price. Time was when diseases of the liver and bile ducts were dealt with in one moderately priced volume, now one has to pay a large sum for a book on the bile ducts alone. This general tendency toward expensive books on limited clinical subjects is to be deplored. If the physician has to buy separate treatises on numerous conditions, such as pneumonia, arterial occlusion of the legs and angina pectoris, the problem of the library becomes difficult, and with few exceptions these narrow clinical monographs contain much inert padding.

Die Ergebnisse der Sternalpunktion By Norbert Henning and Heinz Keilhack Price, 12 marks Pp 90, with 19 illustrations (some in color) Berlin Julius Springer, 1939

The merits of sternal puncture technic for the study of human bone marrow have received considerable attention in the past few years. Monographic studies of Nordenson (1935) and Segerdahl (1935) have been previously reviewed in the ARCHIVES OF INTERNAL MEDICINE. This monograph brings the literature on this subject up to date, and a commendable bibliography is appended. Sternal puncture is undoubtedly here to stay as a diagnostic procedure. Now that the wave of enthusiasm over a new technic has subsided and the limitations of this method have been closely demarcated by those still advocating a complete biopsy technic, clinicians have settled back to find that bone marrow studies are of only relatively rare diagnostic importance. Bone marrow puncture studies in cases of pernicious anemia, hemolytic icterus, polycythemia, agnucytosis, purpura and ordinary leukemia, while informative and constructive in helping formulate ideas concerning the underlying pathologic function of these conditions, are not necessary to a clinical diagnosis. The true diagnostic value of sternal puncture (marrow) lies in the realms of aleukemic leukemia, multiple myelomas, Gaucher's disease and the so-called refractory anemias. Even in cases of these disorders negative findings are in no way conclusive. For those interested in hematology, this monograph is to be recommended.

Abortive Poliomyelitis By Dr Otto Gsell Price, 6.70 marks Pp 93, with 13 illustrations and 19 tables Leipzig Georg Thieme, 1938

The author considers a number of phases of poliomyelitis. After a brief introduction and historical background, the epidemiology is discussed at some length, not only in regard to local epidemics but also in regard to those of other parts of the world, e. g., Denmark and California. The benign course of the disease in the California epidemic is pointed out as in contrast to the high degree of infectivity. The greater the incidence of poliomyelitis from year to year, the more prevalent the abortive form is apt to be.

Pharyngitis and signs of infection of the respiratory tract are associated with the purely abortive form, which clinically often has no nervous system manifestations. The meningitis of Bang's disease, of Weil's disease, of syphilis and of infectious exanthema, are considered with respect to differential diagnosis. The prognosis of the purely abortive form is good, the temperature falls in three to five days, and clinical recovery is apparent in one to two weeks, with no residual signs. A short chapter is devoted to the prophylaxis and treatment of poliomyelitis.

This monograph should be of particular interest to those who are active in this field.

The Vasomotor System in Anoxia and Asphyxia. A Study of the Adjustment Reactions of the Mammalian Organism. By Ernst Gellhorn, M.D., Ph.D., and Edward H. Lambert, M.D. Joint Contribution from the Department of Physiology of the College of Medicine of the University of Illinois and from the Psychiatric Institution of the State Department of Public Welfare. Paper, \$1.00. Pp. 69, with 21 figures. Urbana, Ill.: University of Illinois Press, 1939.

This is a monograph which records the results of experimental observations concerning the effect of both anoxia and asphyxia on the vasomotor mechanism. The authors sharply distinguish between these two conditions, and according to the results of their studies such distinction must be made between the mere absence of oxygen and the absence of oxygen combined with the presence of carbon dioxide. The methods of study are carefully given and the results evaluated. The modes of action of the vasomotor system are considered and explained. Carotid sinus reflexes and the respiratory and circulatory adjustment to the experimental conditions are discussed in detail. The bibliography is extensive and complete.

Blood Groups and Blood Transfusion. By Alexander S. Wiener. Price, \$5. Second edition. Pp. 306, with 25 figures and 84 tables. Springfield, Ill., and Baltimore: Charles C. Thomas, 1939.

This handsome monograph, finely printed and well illustrated, covers the subject of blood groups and blood transfusion in a thoroughly satisfying way. There are definitive discussions of the history of the subject, of the practical aspects of blood typing and of the technic of transfusion. The scholarly chapters on the heredity of the blood group may be fairly heavy going for clinical readers but are invaluable for reference. The book is well documented throughout with references to the literature.

INDEX TO VOLUME 66

Book Reviews and Obituaries are grouped together and are indexed under those headings in alphabetical order under the letters B and O

- Abdomen** See also Gastrointestinal Tract
abdominal syndromes of hypophysial origin, 999
malaria simulating acute surgical diseases of 1004
pain in connection with gastrointestinal or intra-abdominal disease, 996
sensibility of peritoneal surface, 997
- Abnormalities and Deformities** See under names of organs and regions
- Abscess** See also under names of organs and regions, as Brain, abscess, etc
formation of periesophageal cervicomedias-tinal abscesses following nonperforative instrumental trauma to esophagus, 927
- Acacia** See under Kidneys
- Accommodation** See Eyes, accommodation and refraction
- Acetylbetamethylcholine Chloride** See Choline and Choline Derivatives
- Acetylcholine** See Choline and Choline Deriva-tives
- Acid, Ascorbic** See Vitamins, C
Cervitamic See Vitamins, C
effects of acid and of alkali on gastric motor activity, 903
fatty, relation of fatty acids and bile salts to formation of gallstones, 1087
hydrochloric, absorption in stomach, 906
- Addison's Disease**, electrolyte balance during treatment, crises and severe infection in cases of Addison's disease, action of adrenal cortical extracts, 1052
- Adrenal Preparations**, electrolyte balance during treatment, crises and severe infection in cases of Addison's disease, action of adrenal cortical extracts, 1052
- Adrenals**, effects of anterior lobe of pituitary body on adrenal glands, 251
spontaneous hypoglycemia due to atrophy of adrenal glands, report of case 531
- Agranulocytosis** See Granulocytopenia
- Air Passages** See Respiratory Tract
- Albumin** See Blood, proteins
- Alcoholism**, relation between multiple peripheral neuropathy and cirrhosis of liver, 161
- Alimentary Tract** See Digestive Tract
- Alkali**, effects of acid and of alkali on gastric motor activity, 903
- Alving, A S** Practical method for measure-ment of glomerular filtration rate (inulin clearance) with evaluation of clinical sig-nificance of this determination, 306
- Amebiasis**, review of literature, 983
- Amputation**, 773
- Anacidity** See Stomach, acidity
- Anemia, Agranulocytic** See Granulocytopenia
depressant effect of gastric juice obtained from patients with pernicious anemia, 901
effects of gastric mucin on regeneration of hemoglobin in anemic dogs, 902
experiments on properties of extrinsic factor and on reaction of Castle, 1191
splenic, Banti syndrome (fibrocongestive splenomegaly), definition, classification and pathogenesis, 879
splenic, Gaucher's disease, Hand-Schuller-Christian disease and Niemann-Pick dis-ease, 213
- Anesthesia**, effect of anesthetics on gastroin-testinal motility, review of literature, 921
- Aneurysm and angiomas**, 767
intracranial, and syphilis, 1167
of pulmonary artery and syphilis, 1167
review of recent literature, 729
syphilitic, 1167
- Angina, Agranulocytic** See Granulocytopenia
- Angioma and aneurysms**, 767
- Anoxia** See Oxygen, deficiency
- Aorta**, association of syphilis with rupture of, 1165
pathogenesis of aortic insufficiency, 1165
Syphilis See Aortitis, syphilitic
- Aortic Valve**, syphilis, and bacterial endo-carditis, 441
- Aortitis, syphilitic**, roentgenologic examination in diagnosis of, 1168
- Apparatus**, arterial blood pressure in cases of auricular fibrillation, measured directly, 625
significance of albumin-globulin ratio of serum, 295
- Appendicitis**, 973
chronic, 503
- Argyll Robertson Pupils** See under Pupils
- Armies** See under Medicine
- Arrhythmia** arterial blood pressure in cases of auricular fibrillation, measured directly, 625
- Arsenic and Arsenic Compounds** See also Arsphenamines, Tryparsamide
arsenical dermatitis, effect of treatment of syphilis, 1145
purpura haemorrhagica due to arsphenamines sensitivity in patients as influenced by vitamin C therapy, 319
reactions to mapharsen, effects of treatment of syphilis, 1151
- Arsphenamines** See also under Syphilis
purpura haemorrhagica due to, sensitivity in patients as influenced by vitamin C therapy, 319
reactions to neoarsphenamine, effects of treatment of syphilis, 1151
sodium dehydrocholate as solvent for neo-arsphenamine, effect of treatment of syphilis, 1150
- Arteries** See also Aneurysm, Aorta, Arterio-sclerosis, Blood pressure, Blood vessels, Embolism, Periarteritis, Pulse, Throm-bosis, etc
arteriography, 717
inflammation See also Periarteritis
inflammation, arteritis of temporal vessels, report of case, 384
inflammation, temporal arteritis, review of recent literature, 729
oscillometric readings in cases of arterio-sclerotic disease of lower extremity, sig-nificance and interpretation, 155
structural changes in arterioles of myocardium in diffuse arteriolar disease with hyper-tension group 4, 579
- Arteriography** See under Arteries
- Arteriosclerosis** oscillometric readings in cases of arteriosclerotic disease of lower extrem-ity, significance and interpretation, 155
renal hypertension (Goldblatt) and unilateral malignant nephrosclerosis, 541
review of recent literature, 726
- Arteritis** See Arteries, inflammation
- Arthritis, rheumatoid** review of literature, 500
- Ascorbic Acid** See Vitamins C
- Atlas, L N** Oscillometric readings in cases of arteriosclerotic disease of lower extrem-ity, significance and interpretation, 155
- Atrophy** See under names of organs and re-gions, as Adrenals, Spleen, etc

- Atropine sulfate, physiologic effects on alimentary tract, 917
- Auricular Fibrillation See Arrhythmia
- Bacteria See also Staphylococci, Streptococci, Viruses, etc
 coli, sulfanilamide in infection with, 490
 mucosus capsulatus group, sulfanilamide in infection, 490
 Shigella See Dysentery
- Ballinger, J Hypertension (Goldblatt) and unilateral malignant nephrosclerosis, 541
- Banti's Disease See Anemia, splenic
- Barbital and Barbital Derivatives, effect of barbiturates on gastric secretion, 899
 physiologic effects of evipal (C-C-cyclohexenyl-N-methyl-barbituric acid) on alimentary tract, 917
 physiologic effects of seconal (sodium propylmethylcarbonylallylbarbiturate) on alimentary tract, 917
- Bargen, J A Multiple primary malignant lesions of large bowel, 1331
- Basophilism See under Pituitary Body
- Beck, W C Vascular diseases, review of some of recent literature, with critical review of surgical treatment, 707
- Berman, L Primary tumor of inferior vena cava, with clinical features suggestive of Chiari's disease, 50
- Bethell, F H Blood, review of recent literature, 173
- Bile, relation of fatty acids and bile salts to formation of gallstones, 1087
- Bile Ducts See Gallbladder
- Biliary Tract See Gallbladder, Liver
- Bilirubinemia See Blood, bilirubin
- Binger, M W Acacia in treatment of nephrotic syndrome, 1252
- Bismarsen See under Arsenic and Arsenic Compounds
- Bismuth and Bismuth Compounds See also Syphilis
 bismuth and hepatic necrosis effects of treatment of syphilis, 1152
 bismuth and lead in treatment of syphilis, 1143
 bismuth in tissues in treatment of syphilis, 1142
 local tolerance of injected bismuth in treatment of syphilis, 1143
- Bladder, neurogenic, 1170
- Blanchard E L Measurement of vitamin A status of young adults by dark adaptation technique, 661
- Bloch, R G Bronchogenic carcinoma with reference to results with roentgen therapy, 39
- Blood See also Erythrocytes Hemoglobin and Hemoglobin Compounds, etc
 bilirubin, studies of blood in congestive heart failure with reference to reticulocytosis, erythrocyte fragility, bilirubinemia, urobilinogen excretion and changes in blood volume, 1230
 Circulation See also Arteries, Capillaries, Cardiovascular Diseases, Heart, Veins, etc
 circulation, syndrome of subnormal circulation in ambulatory patients, 1095
 circulation time, 713
 Diseases See Anemia Leukemia, etc
 hematologic methods, 220
 lipase, diagnostic significance of determinations of, 62
 pressure, arterial, in cases of auricular fibrillation, measured directly, 625
 pressure, high, arterial hypertension, 748
 pressure, high, body build and hypertension, 393
 pressure high, hypertension (Goldblatt) and unilateral malignant nephrosclerosis, 541
- Blood—Continued
 pressure, high, relative significance of concentration of inorganic sulfate in serum and of its renal clearance with reference to diffuse arteriolar disease with hypertension, 816
 pressure, high, structural changes in arterioles of myocardium in diffuse arteriolar disease with hypertension group 4, 579
 pressure, high, surgical treatment of hypertension, 771
 pressure, normal, 848
 pressure, oscillometry, 717
 pressure, tissue pressure, 717
 proteins significance of albumin-globulin ratio of serum, 295
 ratio of blood and spinal fluid reagin content, 1126
 relation of blood carbon dioxide and dehydration to gastric acidity, 898
 relative significance of concentration of inorganic sulfate in serum and of its renal clearance with reference to diffuse arteriolar disease with hypertension, 816
 review of recent literature, 173
 sugar influence of thiamine on blood sugar levels in diabetic patients, 1079
 sugar, spontaneous hypoglycemia due to atrophy of adrenal glands, report of case, 531
- Vessels See also Arteries, Capillaries, Periarthritis, Veins, etc
 vessels, heparin in surgical treatment of, 765
 volume, studies of blood in congestive heart failure with reference to reticulocytosis erythrocyte fragility, bilirubinemia urobilinogen excretion and changes in blood volume, 1230
- Blumgart, H L Studies of blood in congestive heart failure with reference to reticulocytosis, erythrocyte fragility, bilirubinemia urobilinogen excretion and changes in blood volume, 1230
- Bockus, H L Diagnostic significance of determinations of serum lipase 62
- Body build and hypertension, 393
- Bogardus, G Bronchogenic carcinoma with reference to results with roentgen therapy, 39
- Bones, changes observed roentgenologically, 1179
 Diseases See Osteitis, etc
 marrow, 214
- BOOK REVIEWS
- Abortive Poliomyelitis, O Gsell, 1359
- Anatomic Factors in Hemorrhoids and Varicose Veins of Lower Extremities, G N Alexandrov, 783
- Angina Pectoris Nerve Pathways, Physiology Symptomatology and Treatment, H R Miller, 780
- Aparato circolatorio, P Cossio, 1190
- Architecture of Kidney in Chronic Bright's Disease, J Oliver 292
- Blood Groups and Blood Transfusion, A S Wiener, 1360
- Brucellosis in Man and Animals, I F Huddleston and others, 1358
- Cardiovascular Diseases Their Diagnosis and Treatment, D Scherf and L J Boyd, 781
- Clinical Roentgenology of Alimentary Tract J Buchstein, 1357
- Clinics on Secondary Gastro-Intestinal Disorders Reciprocal Relationships, J Friedenwald, T H Morrison and S Morrison, 779
- Consolidated Indices, 293
- Diat-und Insulinbehandlung der Zuckerkrankheit, F Depisch, 294
- Diagnosis and Management of Diseases of Biliary Tract R F Carter, C H Greene and J R Twiss, 1189

Book Reviews—Continued
 Diagnostic Signs, Reflexes and Syndromes,
 W E Robertson and H F Robertson, 1188
 Diseases of Gallbladder and Bile Ducts, W
 Wilets and A M Snell 1359
 Do You Want to Become a Doctor? M Fish-
 bein, 1188
 Endocrinology in Modern Practice, W Wolf,
 784

Ergebnisse der physikalisch-diätetischen Ther-
 apie, edited by H Lampert, 1189
 Ergebnisse der Sternalpunktion, N Henning
 and H Keilhack, 1359
 Etude morphologique et biologique sur les
 flagelles intestinaux parasites des murides
 Etude comparative des flagelles du cobaye,
 L Morenas 294
 Feinsten Blutgefasse des Menschen, O Mul-
 ler, 1190

General Tissue and Humoral Response to
 Avirulent Tubercle Bacillus Including
 Growth Characteristics of Organism S R
 Rosenthal, 782
 Grundlagen der neuzeitlichen Ernährung des
 Deutschen Menschen Ein Leitfaden für
 Studierende und Ärzte, F Beitram 292
 Hypertension arterial neflogena, J C Fasci-
 olo, 1356
 Hospital Care of Neurosurgical Patients W
 B Hamby, 1190
 Hypertension and Nephritis, A M Fishberg
 530

Introduction to Medical Mycology, G W
 Lewis and M E Hopper, 1006
 Introduction to Ophthalmology, P C Kion-
 feld, 783
 Ischias, H-G Scholtz, 1008
 Letters à un jeune praticien, sur les maladies
 de l'anus et du rectum R Savignac, 781
 Maladies de l'intestin, R Bensaude and
 others, 1009
 Materia Medica, Drug Administration and
 Prescription Writing, O W Bethca, 1189
 Medical Jurisprudence and Toxicology, W D
 McNally, 784
 Medicine d'urgence Symptomes, diagnostic,
 traitement immédiat, formulaire, J Oddo,
 783

Micro-Diffusion Analysis and Volumetric
 Error, E J Conway, 1008
 Mielosi eritremica acuta (malattia di Gugli-
 elmo), A Baserga, 1007
 Neurogenic Bladder, F C McLellan, 1010
 Nitrous Oxide-Oxygen Anesthesia, F W Cle-
 ment, 1009
 Office Gynecology, J P Greenhill, 1010
 Peripheral Vascular Diseases Diagnosis and
 Treatment, W S Collens and N D Wilen-
 sky, 1008

Practical Bacteriology, Haematology and Ani-
 mal Parasitology, E R Stitt, P W Clough
 and M C Clough, 291
 Proctoscopic Examination and Diagnosis and
 Treatment of Diarrheas, M H Streicher,
 1188
 Provoked Alimentary Hyperglycemia Mecha-
 nism of Tolerance Test, J M Flint 778
 Roentgen Technique, C McNeill, 1007
 Rural Medicine, edited by G M Mackenzie,
 529

Sex and Internal Secretions Survey of Recent
 Research, E Allen, C H Danforth and
 E A Doisy 782
 Simplified Diabetic Manual, A Rudy 1010
 Syphilis and Its Accomplices in Mischief
 Society, State and Physician, G M Kat-
 sarnos, 777
 Textbook of Bacteriology, H Zinsser and
 S Bayne-Jones, 1009
 Textbook of Medicine, edited by J J Cony-
 beare, 529
 Textbook of Pathology Correlation of Clini-
 cal Observations and Pathological Findings
 C W Duval and H J Schittenberg, 527

Book Reviews—Continued
 Treatment of Rheumatism in General Prac-
 tice, W S C Copeman, 528
 Vasomotor System in Anoxia and Asphyxia
 Study of Adjustment Reactions of Mam-
 malian Organism, E Gellhorn and E H
 Lambert, 1360
 Verhandlung der Deutschen Gesellschaft für
 Kreislaufforschung, 1358

Botulism, review of literature, 515
 Bowers, J M Arteritis of temporal vessels,
 report of case, 384
 Brain See also Hypothalamus, Nervous Sys-
 tem etc
 abscess (paradoxical) accompanying congenital
 heart disease, report of 2 cases, 1282
 function of frontal areas of human brain,
 1347

Breast cancer, subacute cor pulmonale, 1221
 role of interior lobe of pituitary body with
 respect to mammary gland, 245
 Bright's Disease See Nephritis
 Brown, C F G Relation of fatty acids and
 bile salts to formation of gallstones, 1087
 Brown, E G Evaluation of vitamin B therapy
 for diabetes 679
 Brucer, M Body build and hypertension, 393
 Buchbinder, W C Arterial blood pressure in
 cases of auricular fibrillation, measured
 directly, 625

Calcium and Calcium Compounds, relation
 between disturbances of digestive tract and
 alterations in calcium metabolism 1000
 Calculi See Gallbladder
 Cancer See under names of organs and regions,
 as Breast, Esophagus, Lungs, Rectum,
 Stomach, etc

Capillaries, 715 See also Blood, vessels
 Carbohydrates See also Dextrose, etc
 fecal residue of fat protein and carbohydrate
 in normal dog, 914
 metabolism, role of pituitary body in, 226
 Cardiospasm See under Stomach
 Cardiovascular Diseases See also Blood vessels,
 Heart

pneumococcal pneumonia, analysis of records
 of 1,469 patients treated in Los Angeles
 County Hospital from 1934 through 1938
 outcome and character of pneumonia in
 presence of associated or concomitant con-
 ditions, 1317
 syphilis, 1163

Cardiovascular System
 vessels, Heart, etc See Arteries, Blood
 Celiac Disease, 1002
 pancreatic function in case of nontropical
 sprue, 833
 Cerebrospinal Fluid, examination of, 1125
 ratio of blood and spinal fluid reigin con-
 tent, 1126

Charcot Joints See Tabes Dorsalis
 Chemotherapy See Communicable Diseases,
 Pneumonia, etc
 Chari Syndrome See Thrombophlebitis, hepatic
 Childs, A Pancreatic function in case of non-
 tropical sprue, 833
 Chlorides electrolyte balance during treatment
 crises and severe infection in cases of
 Addison's disease, action of adrenal cortical
 extracts, 1052

Cholelithiasis See Gallbladder, calculi
 Choline and Choline Derivatives See also Bile
 pancreatic secretion in man after stimulation
 with secretin and acetylcholine
 chloride, comparative study, 688
 physiologic effects of acetylcholine on alimen-
 tary tract, 919
 Chorlomeningitis See Meningitis
 Christian-Schuller Syndrome See Schuller-
 Christian Syndrome
 Clavicle clavicular sign (Higoumenakis' sign)
 1179

- Cobb, S Review of neuropsychiatry for 1940, 1341
- Colitis, ulcerative, 989
- Colon See also Gastrointestinal Tract, Intestines
diverticula, 966
lumbocostal neuralgias of colonic origin, 998
secretion by colonic mucosa, 914
tumors, 969
- Comfort, M W Pancreatic secretion in man after stimulation with secretin and acetyl-beta-methylcholine chloride comparative study, 688
- Communicable Diseases See also Meningitis, Syphilis, etc
chemotherapy 478
infectious diseases, review of significant publications in 1939-1940 478
- Consolazio, W V Diabetes insipidus associated with diabetes mellitus metabolic studies and report of case, 607
- Coombs F S Diabetes insipidus associated with diabetes mellitus, metabolic studies and report of case 607
- Cor Pulmonale See Heart, dilatation
- Cornea, keratoplasty, 1185
- Cragg R W Spontaneous hypoglycemia due to atrophy of adrenal glands, report of case 531
- Crime and Criminals, syphilis among criminals 1135
- Cushing's Syndrome See Pituitary Body
- Cysts See under names of organs and regions
- Cytomycosis See Histoplasmosis
- Dark Adaptation See Eyes, accommodation and refraction
- Darling's Disease See Histoplasmosis
- Davis, J S, Jr Diagnosis and treatment of gonorrheal septicemia and gonorrheal endocarditis, 418
- Death Rate See Infant Mortality
- Deficiency Diseases See under Diet and Dietetics, Vitamins etc
- Degeneration, fatty, of heart causing myocardial insufficiency, report of case, 603
- Deglutition disorders, Plummer-Vinson syndrome 926
- Dehydration, relation of blood carbon dioxide and dehydration to gastric acidity, 898
- Dementia Paralytica, physical and mental growth in juvenile dementia paralytica 1183
- Dementia Praecox, developments in insulin therapy 1344
effect of insulin on gastric secretion 897
- Dermatitis arsenical, effect of treatment of syphilis 1145
- Dermatomyositis and diseases in muscles 345
and systemic lupus erythematosus clinical report of 'transitional' cases with consideration of lead as possible etiologic factor 109
and systemic lupus erythematosus comparative study of essential clinicopathologic features, 339
cutaneous lesions, 341
wire loop lesions, 1005
- de Takats, G Vascular diseases, review of some of recent literature, with critical review of surgical treatment 707
- Dextrose See also Blood, sugar, Carbohydrates etc
absorption in stomach, 905
- Diabetes Insipidus See also Schuller-Christian Syndrome
and posterior lobe of pituitary body, 277
associated with diabetes mellitus, metabolic studies and report of case, 607
gastric analyses and gastric symptoms in 999
- Diabetes Mellitus See also Blood sugar
and syphilis, study of 258 cases, 1011
basal insulin requirement in 78
- Diabetes Mellitus—Continued
diabetes insipidus associated with diabetes mellitus, metabolic studies and report of case, 607
evaluation of vitamin B therapy, 679
influence of thiamine on blood sugar levels in diabetic patients, 1079
necrobiosis lipoidica diabetorum 851
protamine zinc insulin, clinical study, report of group of diabetic patients in whose cases glycosuria was disregarded for 1 year, 670
pulmonary infection and necrosis in, report of case of dissecting necrotic pneumonia complicating pancreatic lithiasis, 561
survey of, statistical data and control comparisons with various insulins, 465
- Diarrhea See also Dysentery
review of literature, 978
- Dick, G T Pancreatic function in case of nontropical sprue, 833
- Diet and Dietetics, spinal osteomalacia apparently due to dietary deficiency or digestive disturbances 1001
- Digestive Tract See also Gastrointestinal Tract Intestines, Stomach, etc
relation between disturbances of digestive tract and alterations in calcium metabolism 1000
- Diphenylacetyl diethylaminoethanolhydrochloride (tiasentin) physiologic effects on alimentary tract 918
- Diverticula See Colon Stomach etc
- Dolkait R E Relation of fatty acids and bile salts to formation of gallstones 1087
- Drugs, effect on peripheral circulation 718
- Duary D R Basal insulin requirement in diabetes mellitus 78
- Duodenum diseases review of literature 961
- Ulcers See Peptic Ulcer
- Dysentery See also Diarrhea
review of literature, 979
- Ectodermal Defect hereditary ectodermal dysplasia 1179
- Edema See also under Extremities
reacia in treatment of nephrotic syndrome 1252
- Electrocardiogram See Heart, electrocardiography
- Electrolytes electrolyte balance during treatment crises and severe infection in cases of Addison's disease, action of adrenal cortical extracts 1052
- Elephantiasis syphilis as cause of elephantiasis of lip 1162
- Embolectomy See under Embolism
- Embolism See also Thrombosis
and thrombosis, review of recent literature 732
embolectomy 770
- Encephalitis hemorrhagic, effect of treatment of syphilis 1150
review of literature 507
- Endocarditis association of syphilis with bacterial endocarditis 1163
bacterial and syphilis of aortic valve, 441
diagnosis and treatment of gonorrheal septicemia and gonorrheal endocarditis, 418
review of literature 522
sulfonamide in subacute bacterial endocarditis 487
- Energy Exchange See Metabolism
- Engelberg H Oil aspiration (lipoid) pneumonia in adults, clinicopathologic study of 47 cases, 11
- Enteritis See under Intestines
- Eosinophilia, transitory infiltration of lung with eosinophilia Löffler's syndrome 1215
- Epstein N N Purpura hemorrhagica due to arsphenamines sensitivity in patients as influenced by vitamin C therapy 319
- Ernstene A C Pain in shoulder as sequel to myocardial infarction, 800

- Erythema of ninth day, effect of treatment of syphilis, 1146
- Erythrocytes See also Anemia, Hemoglobin and Hemoglobin Compounds, etc
studies of blood in congestive heart failure with reference to reticulocytosis, erythrocyte fragility, bilirubinemia, urobilinogen excretion and changes in blood volume, 1230
- Esophagoscope See under Esophagus
- Esophagus See also Deglutition
benign stricture of, 927
cancer of, 924
diseases of, 924
esophageal spasm as cardiac symptoms, 998
esophagoscopy, 930
formation of periesophageal cervicomedial abscesses following nonperforative instrumental trauma to esophagus, 927
mechanism of ascending fibrosis of, 927
- Essay, Mississippi Valley Medical Society 1941 essay contest, 1355
- Estrogens See also Hormones, sex
gonadotropic substances, 253
- Evipal See Barbitol and Barbitol Derivatives
- Extremities, Blood Supply See also Blood vessels, Raynaud's Disease, Thromboangitis obliterans, etc
blood supply, blood flow, 710
blood supply, critical review of surgical treatment, 762
blood supply, paravertebral block, 763
blood supply, physiology 709
blood supply, sympathectomy in treatment of peripheral vascular disease, 768
blood supply, treatment of peripheral vascular diseases, 741
blood supply, vascular diseases, review of some of recent literature, with critical review of surgical treatment, 707
circulation time, 713
edema, review of recent literature, 740
effect of drugs on, 718
effect of tobacco on peripheral circulation 723
oscillometric readings in cases of arteriosclerotic disease of lower extremity, significance and interpretation, 155
velocity of pulse wave 715
- Eyes accommodation and refraction, measurement of vitamin A status of young adults by dark adaptation technique, 661
- Falconer, E H Purpura hemorrhagica due to arspenamines, sensitivity in patients as influenced by vitamin C therapy, 319
- Fat See also Acid, fatty, Degeneration, fatty, Lipoids
fecal residue of fat protein and carbohydrate in normal dog, 914
malabsorption of, 1001
role of pituitary body in protein and fat metabolism, 236
- Favre-Nicolas' Disease See Lymphogranuloma Venereum
- Feces, fecal residue of fat, protein and carbohydrate in normal dog, 914
impaction, 972
- Fever, Therapeutic See Syphilis
Undulant See Undulant Fever
- Field, H Jr Significance of albumin-globulin ratio of serum, 295
- Fistula, congenital tracheoesophageal fistula without atresia of esophagus, 928
- Food See Diet and Dietetics, Vitamins, etc
- Formine, P Experiments on properties of extrinsic factor and on reaction of Castle, 1191
- Freeman D G Oil aspiration (lipoid) pneumonia in adults, clinicopathologic study of 47 cases, 11
- Freund, R Transitory infiltration of lung with eosinophilia, Löffler's syndrome, 1215
- Friedlander Bacillus See Bacteria, mucosus capsulatus group
- Gallbladder See also Bile
calculi, relation of fatty acids and bile salts to formation of gallstones 1087
diseases, diagnostic significance of determinations of serum lipase, 62
- Gallstones See Gallbladder, calculi
- Garvin C F Comparison of sulfathiazole and sulfapyridine in treatment of pneumococcal pneumonia, 1246
- Fatty degeneration of heart causing myocardial insufficiency, report of case, 603
- Gastric Juice See under Stomach
- Gastritis See Stomach, inflammation
- Gastroenterology, review of literature from July 1939 to July 1940 893, correction, 1355
- Gastrointestinal Tract See also Colon
Digestive Tract, Intestines, Rectum, Stomach, etc
absorption of iron from, 912
effect of anesthetics on gastrointestinal motility, review of literature, 921
gastrointestinal response of children to test meals consisting of various types of milk, 904
mechanism of motor activity of, 907
pain in connection with gastrointestinal or intra-abdominal disease, 996
physiologic effects of various drugs on alimentary tract, 915
- Gastrosocopy See under Stomach
- Gaucher's Disease See Anemia, splenic
- Globulin in Blood See Blood, proteins
- Glycosuria See Urine sugar
- Goldhamer S M Blood, review of recent literature, 173
- Goldman D Electrocardiogram in insulin shock 93
- Gonococci, diagnosis and treatment of gonorrheal septicemia and gonorrheal endocarditis 418
infections, sulfanilamide in, 489
- Gonorrhea diagnosis and treatment of gonorrheal septicemia and gonorrheal endocarditis 418
- Goudsmit, A, Jr Acacia in treatment of nephrotic syndrome, 1252
Relative significance of concentration of inorganic sulfate in serum and of its renal clearance with reference to diffuse interstitial disease with hypertension, 816
- Granulocytopenia, 173
- Greene J A Electrolyte balance during treatment crises and severe infection in cases of Addison's disease, action of adrenal cortical extracts 1052
- Grisham, W H Survey of diabetes statistical data and control comparisons with various insulins, 465
- Groom H E Anatomic foundation of acidity, gastrosocopic study, 1060
- Growth effect of anterior lobe of pituitary body on growth phenomena, 248
- Guerard C R Relation between multiple peripheral neuropathy and cirrhosis of liver, 161
- Haemophilus Influenzae See Influenza
- Hallock, P Primary tumor of inferior vena cava, with clinical features suggestive of Chiari's disease, 50
- Hallstone, V E Pneumococcal pneumonia analysis of records of 1,469 patients treated in Los Angeles County Hospital from 1934 through 1938, character of pneumonia caused by various types of pneumococci, complications, outcome of pneumonia in presence of certain variations in patient and in course of disease, 1290
- Harper, H A Measurement of vitamin A status of young adults by dark adaptation technique, 661
- Headache, 1343

- Heart See also Arrhythmia, Blood, circulation, Endocarditis, etc
 cerebral abscess (paradoxical) accompanying congenital heart disease, report of 2 cases, 1282
 dilatation, subacute cor pulmonale, 1221
 Diseases See also Cardiovascular Diseases, Endocarditis, etc
 diseases, diagnostic significance of determinations of serum lipase, 62
 electrocardiography, electrocardiogram in insulin shock 93
 esophageal spasm as cardiac symptoms, 998
 fatty degeneration of heart causing myocardial insufficiency, report of case 603
 hypertrophy, cause of, 1163
 interauricular septal defect, 807
 pain in shoulder as sequel to myocardial infarction, 800
 pneumococcal pneumonia, analysis of records of 1469 patients treated in Los Angeles County Hospital from 1934 through 1938, outcome and character of pneumonia in presence of associated or concomitant conditions, 1317
 structural changes in arterioles of myocardium in diffuse arteriolar disease with hypertension group 4, 579
 studies of blood in congestive heart failure with reference to reticulocytosis, erythrocyte fragility, bilirubinemia, urobilinogen excretion and changes in blood volume, 1230
 syndrome of subnormal circulation in ambulatory patients 1095
- Hematology See Blood, Hemopoietic System
- Hemoglobin and Hemoglobin Compounds See also Anemia, Blood, Erythrocytes
 effects of gastric mucin on regeneration of hemoglobin in anemic dogs, 902
- Hemopoietic System, hematologic methods 220
- Hemorrhage See Encephalitis, hemorrhagic, Purpura haemorrhagica, etc
- Heparin in surgical treatment of blood vessels, 765
- Hepatitis See under Liver
- Hernia diaphragmatic, 928
 review of literature, 998
- Herpes simplex, review of literature, 509
- Higoumenakis' Sign See Clavicle
- Hildebrand, A G Necrobiosis lipoidica diabetorum, 851
- Histamine anatomic foundation of acidity, gastroscopic study, 1060
 effect on gastric secretion, 899
 gastric acidity after histamine stimulation, 895
 physiologic effects on alimentary tract 919
- Histoplasmosis, reticuloendothelial cytomyces (histoplasmosis of Darling) 520
- Hodgkin's Disease See Lymphogranuloma
- Hormones See also Adrenal Preparations, Estrogens, Insulin etc
 Gonadotropic See Pituitary Preparations
 sex, effect on experimental syphilis, 1117
 Thyrotropic See Pituitary Preparations
- Hospitals, pneumococcal pneumonia, analysis of records of 1,469 patients treated in Los Angeles County Hospital from 1934 through 1938, character of pneumonia caused by various types of pneumococci, complications, outcome of pneumonia in presence of certain variations in patient and in course of disease 1290
 pneumococcal pneumonia analysis of records of 1,469 patients treated in Los Angeles County Hospital from 1934 through 1938 outcome and character of pneumonia in presence of associated or concomitant conditions, 1317
- Hydrophobia See Rabies
- Hyperinsulinism See under Insulin, Pancreas
- Hypertension See Blood pressure, high
- Hypertrophy See under names of organs and regions, as Heart, etc
- Hypoglycemia See Blood sugar
- Hypophysis See Pituitary Preparations
- Hypophysis See Pituitary Body
- Hypothalamus See also Pituitary Body
 influence of hypothalamic stimulation on gastric motility, 905
- Icterus See Jaundice
- Ileus See under Intestines
- Industrial Diseases, lead poisoning in roofers, 1003
 syphilis and industry, 1136
- Infant Mortality, syphilis as cause of fetal and neonatal deaths, 1178
- Infantile Paralysis See Poliomyelitis
- Infection, focal, review of literature, 501
- Infectious Diseases See Communicable Diseases
- Influenza, prevalent influenza-like disease, 498
 review of literature 496
- Insulin See also Diabetes Mellitus, Pancreas
 basal insulin requirement in diabetes mellitus, 78
 developments in therapy of dementia praecox, 1344
 effect on gastric secretion 897
 electrocardiogram in insulin shock, 93
 practical method for measurement of glomerular filtration rate (insulin clearance) with evaluation of clinical significance of this determination, 306
 protamine zinc insulin, clinical study, report of group of diabetic patients in whose cases glycosuria was disregarded for 1 year, 670
 survey of diabetes, statistical data and control comparisons with various insulins, 465
- Intestines See also Colon, Duodenum, Gastrointestinal Tract, Rectum
 absorption of various material, 911
 bacterial and parasitic diseases of, 976
 behavior of gastrointestinal tract in lead poisoning, 1003
 diseases, diagnostic significance of determinations of serum lipase, 62
 experimental study on intestinal motility in mechanical ileus, 910
 large, diseases of, review of literature, 965
 malabsorption of fat, 1001
 multiple primary malignant lesions of large bowel 1331
 obstruction, review of literature, 962
 parasites 982
 polyps, 967
 regional enteritis, 987
 renal calcification accompanying pyloric and high intestinal obstruction 1000
 rhythmic contractions of, 908
 roentgen study and other diagnostic procedures, 992
 small, diseases of, 961
- Ireland, R M Pneumococcal pneumonia analysis of records of 1,469 patients treated in Los Angeles County Hospital from 1934 through 1938, character of pneumonia caused by various types of pneumococci, complications, outcome of pneumonia in presence of certain variations in patient and in course of disease, 1290
- Iron, absorption of iron from gastrointestinal tract, 912
- Isaacs R Blood, review of recent literature 173
- Islands of Langerhans See Pancreas
- Jaundice and hepatitis, effects of treatment of syphilis, 1147
- Johnson, T A Diagnostic significance of determinations of serum lipase, 62
- Johnston, G W Electrolyte balance during treatment, crises and severe infection in cases of Addison's disease action of adrenal cortical extracts, 1052
- Jonas L Syndrome of subnormal circulation in ambulatory patients, 1095

- Jones, C M Gastroenterology, review of literature from July 1939 to July 1940, 893, correction, 1355
- Jones, K K Relation of fatty acids and bile salts to formation of gallstones, 1087
- Joslin, E P Diabetes mellitus and syphilis, study of 258 cases, 1011
- Kaplan, A Cerebral abscess (paradoxical) accompanying congenital heart disease, report of 2 cases, 1282
- Kaufman, R E Influence of thiamine on blood sugar levels in diabetic patients, 1079
- Keil, H Dermatomyositis and systemic lupus erythematosus, clinical report of "transitional" cases, with consideration of lead as possible etiologic factor, 109
- Dermatomyositis and systemic lupus erythematosus, comparative study of essential clinicopathologic features, 339
- Keith, N M Relative significance of concentration of inorganic sulfate in serum and of its renal clearance with reference to diffuse arteriolar disease with hypertension, 816
- Renal involvement in disseminated lupus erythematosus, 643
- Keratitis, interstitial, 1182
- Interstitial, treatment, 1183
- Keratoplasty See under Corner
- Kidneys, acacia in treatment of nephrotic syndrome, 1252
- Diseases See Nephritis
- function tests, practical method for measurement of glomerular filtration rate (inulin clearance) with evaluation of clinical significance of this determination, 306
- relative significance of concentration of inorganic sulfate in serum and of its renal clearance with reference to diffuse arteriolar disease with hypertension, 816
- renal calcification accompanying pyloric and high intestinal obstruction, 1000
- renal involvement in disseminated lupus erythematosus, 643
- Kinell, J Pain in shoulder as sequel to myocardial infarction, 800
- Kistler, M Pneumococcal pneumonia, analysis of records of 1,469 patients treated in Los Angeles County Hospital from 1934 through 1938 character of pneumonia caused by various types of pneumococci, complications, outcome of pneumonia in presence of certain variations in patient and in course of disease, 1290
- Klemperer, P Wire loop lesions, 1005
- Lactation See also Milk
- role of anterior lobe of pituitary body with respect to mammary gland, 245
- Langerhans' Islands See under Pancreas
- Lead and bismuth in treatment of syphilis, 1143
- dermatomyositis and systemic lupus erythematosus, clinical report of "transitional" cases, with consideration of lead as possible etiologic factor, 109
- poisoning, behavior of gastrointestinal tract in, 1003
- poisoning in roofers, 1003
- Leiomyosarcoma, primary tumor of inferior vena cava, with clinical features suggestive of Chiari's disease, 50
- Leptospirosis See Spirochetosis
- Leukemia, biologic and etiologic aspects, 195
- chemical and pathologic picture, 202
- clinical data, 206
- experimental, in animals, 199
- myelogenous, intestinal ulceration in, 1004
- treatment, 210
- Lipase See under Blood
- Lipoid Histiocytosis See Niemann's Disease
- Lipoids See also Fat
- necrobiosis lipoidica diabetorum, 851
- Pneumonia See Pneumonia
- Lithiasis See Gallbladder, calculi, Pancreas, calculi
- Liver, Banti syndrome (fibrocongestive splenomegaly), definition, classification and pathogenesis, 879
- bismuth and hepatic necrosis, effects of treatment of syphilis, 1152
- cirrhosis, relation between multiple peripheral neuropathy and cirrhosis of liver, 161
- diseases, diagnostic significance of determinations of serum lipase, 62
- hepatitis and jaundice, effects of treatment of syphilis, 1147
- hepatitis in early syphilis, 1156
- Loeffler Syndrome See Eosinophilia, Lungs, pathology, Tuberculosis, pulmonary
- Lorenz, M Relation of fatty acids and bile salts to formation of gallstones, 1087
- Los Angeles County Hospital, pneumococcal pneumonia, analysis of records of 1,469 patients treated in Los Angeles County Hospital from 1934 through 1938, character of pneumonia caused by various types of pneumococci, complications, outcome of pneumonia in presence of certain variations in patient and in course of disease, 1290
- pneumococcal pneumonia, analysis of records of 1,469 patients treated in Los Angeles County Hospital from 1934 through 1938, outcome and character of pneumonia in presence of associated or concomitant conditions, 1317
- Lungs See also Respiratory Tract
- cancer, bronchogenic carcinoma with reference to results with roentgen therapy, 39
- cancer, effects of roentgen therapy on histologic picture and on survival in cases of primary carcinoma of lung, 140
- pathology, transitory infiltration of lung with eosinophilia, Loeffler's syndrome, 1215
- pulmonary infection and necrosis in diabetes mellitus, report of case of dissecting necrotic pneumonia complicating pancreatic lithiasis, 561
- Tuberculosis See Tuberculosis, pulmonary
- Lupus erythematosus and diseases in muscles, 345
- erythematosus, cutaneous lesions, 341
- erythematosus, dermatomyositis and systemic lupus erythematosus, clinical report of "transitional" cases, with consideration of lead as possible etiologic factor, 109
- erythematosus, dermatomyositis and systemic lupus erythematosus, comparative study of essential clinicopathologic features, 339
- erythematosus, disseminated, renal involvement in, 643
- erythematosus, wire loop lesions, 1005
- Lymph Nodes, Hodgkin's disease, lymphosarcoma and lymphomatoid diseases, 187
- Lymphedema See Elephantiasis
- Lymphocytes in Meningitis See Meningitis
- Lymphogranuloma, Hodgkin's disease, lymphosarcoma and lymphomatoid diseases, 187
- Lymphogranuloma Venereum as cause of rectal disease, 992
- Lymphosarcoma, Hodgkin's disease and lymphomatoid diseases, 187
- McDaniel, L T Diabetes mellitus and syphilis, study of 258 cases, 1011
- Maguire, J F Pneumococcal pneumonia, analysis of records of 1,469 patients treated in Los Angeles County Hospital from 1934 through 1938, outcome and character of pneumonia in presence of associated or concomitant conditions, 1317
- Malaria, review of literature, 518
- simulating acute surgical diseases of abdomen, 1004
- treatment of malaria inoculata, 1177
- Mapharsen See Arsenic and Arsenic Compounds
- Marks, H H Diabetes mellitus and syphilis, study of 258 cases, 1011

- Martin, H Basal insulin requirement in diabetes mellitus, 78
- Mason, D G Subacute cor pulmonale, 1221
- Mason, H L Observations on induced thiamine (vitamin B₁) deficiency in man 785
- Meat experiments on properties of extrinsic factor and on reaction of Castle, 1191
- Medicine, syphilis and national defense, 1130
- Melnick, D Significance of albumin-globulin ratio of serum, 295
- Meningitis, lymphocytic choriomeningitis, review of literature, 508
- Merritt, W H Oil aspiration (lipoid) pneumonia in adults, clinicopathologic study of 47 cases, 11
- Metabolism, diabetes insipidus associated with diabetes mellitus metabolic studies and report of case, 607
- Milk, gastrointestinal response of children to test meals consisting of various types of milk, 904
- Miller, B F Practical method for measurement of glomerular filtration rate (inulin clearance) with evaluation of clinical significance of this determination 306
- Mills, E S Purpura hemorrhagica due to arspenamines, sensitivity in patients as influenced by vitamin C therapy, 319
- Mohr, C F Syphilis, review of recent literature, 1112
- Montgomery H Necrobiosis lipoidica diabetorum 851
- Moolten, S E Pulmonary infection and necrosis in diabetes mellitus report of case of dissecting necrotic pneumonia complicating pancreatic lithiasis 561
- Moore F J Pneumococcal pneumonia analysis of records of 1,469 patients treated in Los Angeles County Hospital from 1934 through 1938, character of pneumonia caused by various types of pneumococci complications, outcome of pneumonia in presence of certain variations in patient and in course of disease 1290
- Pneumococcal pneumonia analysis of records of 1,469 patients treated in Los Angeles County Hospital from 1934 through 1938, outcome and character of pneumonia in presence of associated or concomitant conditions 1317
- Moore J E Syphilis, review of recent literature 1112
- Morphine, physiologic effects on alimentary tract, 916
- Muscles, cervical rib and scalenus syndrome 767
- diseases in dermatomyositis and systemic lupus erythematosus, 345
- myograms 1170
- Myelitis syphilitic transverse myelitis, 1172
- Myeloma multiple, 212
- Myositis and diseases in muscles, 345
- cutaneous lesions 341
- dermatomyositis and systemic lupus erythematosus clinical report of "transitional" cases with consideration of lead as possible etiologic factor 109
- dermatomyositis and systemic lupus erythematosus comparative study of essential clinicopathologic features, 339
- wire loop lesions, 1005
- Navies See under Medicine
- Necrobiosis lipoidica diabetorum 851
- Neosarsphenamine See Arspenamines
- Nephritis and syphilis 1186
- hypertension (Goldblatt) and unilateral malignant nephrosclerosis, 541
- Nephrosclerosis See Arteriosclerosis renal, Nephritis
- Nephrosis See Kidneys diseases Nephritis
- Nerves See also Neuralgia, Neuritis Paralysis optic atrophy, 1169
- Nervous System See also Brain, Nerves, etc paravertebral block in peripheral vascular disease, 763
- Syphilis See under Syphilis
- Neuralgia, lumbocervical, of colonic origin, 998
- Neuritis, relation between multiple peripheral neuropathy and cirrhosis of liver, 161
- syphilitic polyneuritis 1173
- Neuropathy See Neuritis
- Neuropsychiatry, review for 1940, 1341
- Neurosyphilis See under Syphilis
- Nicolas-Favre's Disease See Lymphogranuloma Venereum
- Niemann's Disease, Gaucher's disease Hand-Schuller-Christian disease and Niemann-Pick disease, 213
- Nissl Bodies See Nissl
- Nutrition See also Diet and Dietetics, Vitamins, etc
- Nuttall, P B Anatomic foundation of acidity, gastroscopic study, 1060
- Obituaries**
- Riggs, Austen Fox, 1346
- Odel H M Structural changes in arterioles of myocardium in diffuse arteriolar disease with hypertension group 4 579
- Oil Pneumonia See Pneumonia
- Oscillometry See under Arteries, Blood pressure
- Osteitis in early syphilis, 1156
- Osteomalacia spinal, apparently due to dietary deficiency or digestive disturbances 1001
- Osterberg A J Pancreatic secretion in man after stimulation with secretin and acetyl-beta-methylcholine chloride, comparative study, 689
- Owens L B Evaluation of vitamin B therapy for diabetes 679
- Oxygen deficiency, effect of anoxia on gastric secretion, 898
- Prachymeningitis hypertrophic 1171
- Pradot P Syphilis review of recent literature 1112
- Pain in connection with gastrointestinal or intrabdominal disease 996
- in shoulder as sequel to myocardial infarction 800
- Palmer, W L Anatomic foundation of acidity, gastroscopic study, 1060
- Palsy See Paralysis
- Panciers calculi pulmonary infection and necrosis in diabetes mellitus report of case of dissecting necrotic pneumonia complicating pancreatic lithiasis 561
- diseases, diagnostic significance of determinations of serum lipase, 62
- pancreatic function in case of nontropical sprue, 833
- pancreatic secretion in man after stimulation with secretin and acetyl-beta-methylcholine chloride, comparative study 689
- Paralysis General See Dementia Paralytica
- Infantile See Poliomyelitis
- pseudobulbar, 1173
- Parnall, C G, Jr Significance of albumin-globulin ratio of serum 295
- Pecora L J Diabetes insipidus associated with diabetes mellitus metabolic studies and report of case, 607
- Peptic Ulcer, intestinal ulceration in myelogenous leukemia 1004
- review of literature, 946
- therapy, review of literature 953
- Periarteritis nodosa, review of recent literature, 731
- Peritonitis sulfanilamide in, 489
- Petrolatum, liquid oil aspiration (lipoid) pneumonia in adults, clinicopathologic study of 47 cases 11
- Pick-Niemann's Disease See Niemann's Disease
- Pitressin See Pituitary Preparations

- Pituitary Body** See also Hypothalamus
abdominal syndromes of hypophysial origin, 999
antihormones, 268
Cushing's syndrome, 274
effect of anterior lobe on growth phenomena, 248
effects of anterior lobe on adrenal glands, 251
gonadotropic substances, 253
posterior lobe and diabetes insipidus, 277
review of literature (1938 and 1939), 226
role in carbohydrate metabolism, 226
role in protein and fat metabolism, 236
role of anterior lobe with respect to mammary gland, 245
Simmonds' disease, 271
- Pituitary Preparations**, effect of anterior lobe of pituitary body on growth phenomena, 248
gonadotropic substances, 253
physiologic effects of hypophysin and pitressin on alimentary tract, 920
thyrotropic hormone, 241
- Plague** review of literature, 506
- Pneumonia**, 492
chemical pneumonia, 493
chemotherapy in, 480
comparison of sulfathiazole and sulfapyridine in treatment of pneumococcal pneumonia, 1246
oil aspiration (lipoid) pneumonia in adults, clinicopathologic study of 47 cases, 11
oil aspiration pneumonia, 493
pneumococcal, analysis of records of 1,469 patients treated in Los Angeles County Hospital from 1934 through 1938 character of pneumonia caused by various types of pneumococci complications, outcome of pneumonia in presence of certain variations in patient and in course of disease, 1290
pneumococcal, analysis of records of 1,469 patients treated in Los Angeles County Hospital from 1934 through 1938 outcome and character of pneumonia in presence of associated or concomitant conditions, 1317
pulmonary infection and necrosis in diabetes mellitus report of case of dissecting necrotic pneumonia complicating pancreatic lithiasis, 561
- Poisons and Poisoning** See under names of substances, as Lead etc
- Polomyelitis**, review of literature, 509
- Polyuria** See Diabetes Insipidus
- Portal Vein**, Banti syndrome (fibrocongestive splenomegaly) definition, classification and pathogenesis, 879
- Posture**, tissue pressure, 717
- Potassium**, electrolyte balance during treatment, crises and severe infection in cases of Addison's disease, action of adrenal cortical extracts, 1052
- Pregnancy and syphilis**, 1177
effect of treatment of syphilis on, 1178
effect on gastric secretion, 896
- Prizes** Mississippi Valley Medical Society contest, 526
- Prostaglandin** physiologic effects on alimentary tract, 921
- Protamine Zinc Insulin** See Insulin
- Protein**, fecal residue of fat, protein and carbohydrate in normal dog, 914
in Blood See Blood, proteins
role of pituitary body in protein and fat metabolism, 236
- Psittacosis**, 515
- Psychiatry** developments in, 1344
- Public Health** aspects of syphilis, 1130
- Pulse** See also Arrhythmia, Blood pressure
velocity of pulse wave, 715
- Pupils** Argyll Robertson, 1168
- Purpura haemorrhagica** due to arsphenamines, sensitivity in patients as influenced by vitamin C therapy, 319
thrombopenic, effect of treatment of syphilis, 1146
- Pylores**, renal calcification accompanying pyloric and high intestinal obstruction, 1000
stenosis, review of literature, 936
- Rabies**, review of literature, 511
- Rat Bite Fever**, review of literature, 522
- Rauiston, B. O.** Pneumococcal pneumonia, analysis of records of 1,469 patients treated in Los Angeles County Hospital from 1934 through 1938, outcome and character of pneumonia in presence of associated or concomitant conditions, 1317
- Ravenna, P.** Banti syndrome (fibrocongestive splenomegaly), definition, classification and pathogenesis, 879
- Raynaud's Disease**, review of recent literature, 731
- Rectum**, cancer, 970
lymphogranuloma venereum as cause of rectal disease, 992
- Refraction** See Eyes, accommodation and refraction
- Reimann, H. A.** Infectious diseases, review of significant publications in 1939-1940, 478
- Respiratory Tract** pneumococcal pneumonia analysis of records of 1,469 patients treated in Los Angeles County Hospital from 1934 through 1938, outcome and character of pneumonia in presence of associated or concomitant conditions, 1317
- Reticulocytes** See Erythrocytes
- Reticuloendothelial System** See also Anemia, Jaundice, etc
reticuloendothelial cytomycosis (histoplasmosis of Darling), 520
- Rheumatic Fever**, association of syphilis with rheumatic heart disease, 1165
review of literature, 500
- Riboflavin** See Vitamins, B
- Ribs**, cervical, and scalenus syndrome, 767
- Rickettsia**, rickettsial diseases, review of literature, 516
rickettsial vaccines, review of literature, 517
- Ridge, G. K.** Pneumococcal pneumonia, analysis of records of 1,469 patients treated in Los Angeles County Hospital from 1934 through 1938, outcome and character of pneumonia in presence of associated or concomitant conditions, 1317
- Robinson, S. C.** Body build and hypertension, 393
- Rockwein, S. S.** Evaluation of vitamin B therapy for diabetes, 679
- Roentgen Rays**, roentgen study and other diagnostic procedures, 992
Therapy See Lungs, cancer
- Roentgenography** See under Roentgen Rays
- Rosenberg, D. H.** Bacterial endocarditis and syphilis of aortic valve, 441
- Rushton, J. G.** Spontaneous hypoglycemia due to atrophy of adrenal glands, report of case, 531
- Ryneerson, E. H.** Review of literature on pituitary body (1938 and 1939), 226
Necrobiosis lipoidica diabetorum, 851
- Salmonella**, toxemia from, 515
- Samuelson, S.** Transitory infiltration of lung with eosinophilia, Löffler's syndrome, 1215
- Saphir, O.** Hypertension (Goldblatt) and unilateral malignant nephrosclerosis, 541
- Sarcoma** See under names of tumors, as Leiomyosarcoma, Lymphosarcoma, etc
- Schindler, R.** Anatomic foundation of anacidity gastroscopic study, 1060
- Schizophrenia** See Dementia Praecox
- Schuller-Christian Syndrome**, Gaucher's disease, Hand-Schuller-Christian disease and Niemann-Pick disease, 213
- Schweiger, L. R.** Multiple primary malignant lesions of large bowel, 1331
Review of literature on pituitary body (1938 and 1939), 226

- Scupham, G W Vascular diseases, review of some of recent literature, with critical review of surgical treatment, 707
- Seconal See under Barbitol and Barbitol Derivatives
- Secretin See under Pancreas
- Septicemia, staphylococci, 1
- Serum See Blood
- Shigella Dysenteriae See Dysentery
- Shoulder, pain in shoulder as sequel to myocardial infarction, 800
- Simmonds' Disease See Pituitary Body
- Smallpox vaccine, 514
- Smith, B Survey of diabetes, statistical data and control comparisons with various insulins, 465
- Smith, B F Observations on induced thiamine (vitamin B₁) deficiency in man, 785
- Smoking See Tobacco
- Sobisminol See under Syphilis
- Societies, American College of Physicians, 784
American Congress of Physical Therapy, 526
American Public Health Association, annual meeting, 1355
Mississippi Valley Medical Society, 526
Second Pan American Congress of Endocrinology, 1355
- Sodium bromide, effect on gastric secretion, 899
dehydrocholate as solvent for neoarsphenamine, effect of treatment of syphilis, 1150
electrolyte balance during treatment, crises and severe infection in cases of Addison's disease, action of adrenal cortical extracts, 1052
propylmethylcarbonylallylbarbiturate (seconal), physiologic effects on alimentary tract, 917
- Thiosulfate See under Syphilis
- Solusalvarsan See under Syphilis
- Spinal Fluid See Cerebrospinal Fluid
- Spine, spinal osteomalacia apparently due to dietary deficiency or digestive disturbances, 1001
- Spirochaeta Pallida See also Syphilis
culture, 1116
distribution of spirochetes in tissue, 1116
in blood in early syphilis, 1117
staining, 1115
- Spirochetosis, leptospirosis, review of literature, 519
- Spleen atrophy, 1002
- Splenomegaly See also Anemia, splenic, Niemann's Disease
Banti syndrome (fibrocongestive splenomegaly), definition, classification and pathogenesis, 879
- Sprue, Nontropical See Celiac Disease
- Stains and Staining of Spirochaeta pallida, 1115
- Stalker, L K Spontaneous hypoglycemia due to atrophy of adrenal glands, report of case, 531
- Staphylococci, infections, sulfanilamide in 488
septicemia, 1
- Starr, I Syndrome of subnormal circulation in ambulatory patients, 1095
- Steatorrhea See Celiac Disease
- Steiner, P E Effects of roentgen therapy on histologic picture and on survival in cases of primary carcinoma of lung, 140
- Stenosis See under Pylorus
- Sternum, Puncture See Bones, marrow
- Stickney, J M Renal involvement in disseminated lupus erythematosus, 643
- Stomach See also Gastrointestinal Tract, Pylorus
absorption of various material, 905
acidity after histamine stimulation, 895
acidity, anatomic foundation of anacidity, gastroscopic study, 1060
acidity, relation between carcinoma of stomach and known reduction of gastric acidity, 900
acidity, relation of blood carbon dioxide and dehydration to gastric acidity, 898
- Stomach—Continued
cancer, relation between carcinoma of stomach and known reduction of gastric acidity, 900
cancer, review of literature, 941
cardiospasm, 925
diseases, diagnostic significance of determinations of serum lipase, 62
diverticula, 910
effects of acid and of alkali on gastric motor activity, 903
experiments on properties of extrinsic factor and on reaction of Castle, 1191
gastric analyses and gastric symptoms in diabetes insipidus 999
gastric emptying time of dogs under conditions of vitamin A deficiency, 905
gastric peristalsis, 903
gastroscopy, review of literature, 930
inflammation, gastritis, review of literature 932
influence of hypothalamic stimulation on gastric motility, 905
miscellaneous considerations, 996
sarcoma, 940
secretion, depressant effect of gastric juice obtained from patients with pernicious anemia, 901
secretion, effect of anoxia on, 898
secretion, effect of insulin on, 897
secretion, effect of pregnancy on 896
secretion, effect of various solutions on 899
secretion, effects of gastric mucin on regeneration of hemoglobin in anemic dogs 902
secretion, physiologic aspects, 893
tone and motility after subtotal resection, 944
tumors, 940
- Ulcers See Peptic Ulcer
volvulus of, 939
- Stools See Feces
- Streptococci, infections, 495
infections, sulfanilamide in, 486
- Strouse, S Basal insulin requirement in diabetes mellitus 78
- Sturgis, C C Blood, review of recent literature, 173
- Sugar in Blood See Blood, sugar
- Sugarman, H Arterial blood pressure in cases of auricular fibrillation, measured directly, 625
- Sulfanilamide and Sulfanilamide Derivatives, Therapy See under Endocarditis, Gonococci, Peritonitis, Pneumonia, Staphylococci, etc
toxicity, granulocytopenia, 173
- Sulfapyridine See Pneumonia
- Sulfathiazole See Pneumonia
- Suprarenal Preparations See Adrenal Preparations
- Suprarenals See Adrenals
- Sutherland, R T Staphylococci septicemia, 1
- Sympathectomy See Extremities, blood supply
- Syntropan (phosphate of 3-diethylamino-2, 2-dimethylpropylester of tropic acid), physiologic effects on alimentary tract, 918
- Syphilis See also under names of organs, regions and diseases, as Aneurysm, Aortic Valve, Aortitis, syphilitic, Cardiovascular Diseases, Neuritis, Thyroid, etc
among criminals, 1135
and aneurysm, 1167
and diabetes mellitus, study of 258 cases, 1011
and industry, 1136
and national defense, 1130
and nephritis, 1186
and pregnancy, 1177
and tuberculosis, 1185
aneurysm of pulmonary artery, 1167
arsphenamine in treatment of 1139
as cause of elephantiasis of lip, 1162
as cause of fetal and neonatal deaths, 1178

Syphilis—Continued

- association with bacterial endocarditis, 1163
- association with rheumatic heart disease, 1165
- association with rupture of aorta, 1165
- biologic false positive serologic reactions for, 1126
- bismuth in tissues in treatment of, 1142
- changes observed roentgenologically in bones, 1179
- clavicular sign, 1179
- congenital, 1179
- congenital, treatment, 1183
- contact investigation, 1154
- control in Memphis, 1134
- control in South, 1134
- culture spirochetes as antigen in serologic tests for, 1121
- daily variation in serum reagin, 1125
- diagnosis of neurosyphilis, 1168
- early, hepatitis in, 1156
- early, osteitis in, 1156
- effect of treatment, 1178
- examination of spinal fluid, 1125
- experimental, effect of sex hormones on, 1117
- experimental fever therapy, 1118
- Hereditary See Syphilis, congenital
- history of, 1112
- immunity in, 1118
- incidence of, 1153
- induced tolerance to arsenic in treatment of, 1140
- infectious relapse, 1155
- infectiousness of early syphilis, 1155
- intracranial aneurysm, 1167
- latent, 1161
- local tolerance of infected bismuth in treatment of, 1143
- massive dose method of treatment, 1157
- neurogenic bladder, 1170
- pathogenesis of aortic insufficiency, 1165
- prognosis of early syphilis, 1160
- public health aspects of, 1130
- purpura haemorrhagica due to arsphenamines, sensitivity in patients as influenced by vitamin C therapy, 319
- ratio of blood and spinal fluid reagin content, 1126
- review of recent literature, 1112
- serodiagnosis of, 1120
- serologic surveys, 1120
- serologic tests in mice, 1120
- sobisminol in treatment of, 1141
- sodium thiosulfate in treatment of, 1144
- solusalsarsan in treatment of, 1140
- Spirochaeta pallida in blood in early syphilis, 1117
- spirocheticidal activity of arsenicals in vitro and in vivo, 1137
- supersensitive serologic tests as guide to cure, 1158
- teaching, 1137
- traumatic, 1162
- treatment of neurosyphilis, 1173
- treatment-resistant, 1156
- tryparsamide in treatment of, 1140
- tuberculosis in syphilitic rabbits, 1119
- untoward effects from fever therapy, 1176
- untoward effects of treatment of, 1145
- vaccine in treatment of, 1144

Tabes Dorsalis, Charcot joints, 1170

- myograms, 1170
- Talbott, J. H. Diabetes insipidus associated with diabetes mellitus, metabolic studies and report of case, 607
- Tetanus, review of literature, 505
- Thiamine See Vitamins, B
- Thomas, R. E. Pneumococcic pneumonia, analysis of records of 1,469 patients treated in Los Angeles County Hospital from 1934 through 1938, character of pneumonia caused by various types of pneumococci, complications, outcome of pneumonia in presence of certain variations in patient and in course of disease 1290

Thomas, R. E.—Continued

- Pneumococcic pneumonia, analysis of records of 1,469 patients treated in Los Angeles County Hospital from 1934 through 1938, outcome and character of pneumonia in presence of associated or concomitant conditions, 1317
- Thromboangitis See also Thrombophlebitis obliterans, review of recent literature, 729
- Thrombopenia See Purpura haemorrhagica
- Thrombophlebitis See also Thromboangitis obliterans, Thrombosis
 - hepatic, primary tumor of inferior vena cava, with clinical features suggestive of Chiari's disease, 50
- Thrombosis See also Embolism, Thrombophlebitis
 - and embolism, review of recent literature 732
 - Banti syndrome (fibrocongestive splenomegaly), definition, classification and pathogenesis, 879
 - surgical treatment of venous thrombosis, 764
- Thyroid syphilis of 1161
- thyrotropic hormone, 241
- Tinney, W. S., Jr. Interauricular septal defect, 807
- Tissue, distribution of spirochetes in, 1116
- pressure, 717
- Tobacco, effect on peripheral circulation, 723
- Tolstoi, E. Protamine zinc insulin, clinical study, report of group of diabetic patients, in whose cases glycosuria was disregarded for 1 year, 670
- Toxoplasmosis, review of literature, 521
- Trasentin (diphenylacetyldiethylaminoethanolhydrochloride), physiologic effects on alimentary tract, 918
- Treloar, A. E. Normal blood pressure, 848
- Tryparsamide, reactions to, effects of treatment of syphilis, 1151
- Tuberculosis and syphilis 1185
 - in syphilitic rabbits, 1119
 - pulmonary, transitory infiltration of lung with eosinophilia, Löffler's syndrome, 1215
 - sulfanilamide in, 489
- Tumors See under names of tumors, as Angioma, Leiomyosarcoma, Lymphosarcoma etc and under names of organs and regions, as Colon, Stomach, etc
- Ulcers, Peptic See Peptic Ulcer
- Undulant Fever, review of literature, 504
- Universities, Bicentennial Conference at University of Pennsylvania, 526
- Urine, studies of blood in congestive heart failure with reference to reticulocytosis erythrocyte fragility, bilirubinemia, urobilinogen excretion and changes in blood volume, 1230
 - sugar, protamine zinc insulin, clinical study report of group of diabetic patients in whose cases glycosuria was disregarded for 1 year, 670
- Urobilin, studies of blood in congestive heart failure with reference to reticulocytosis erythrocyte fragility, bilirubinemia, urobilinogen excretion and changes in blood volume, 1230
- Urobilinogen See under Urine
- Vaccine Therapy See Syphilis
- Van Dellen, T. R. Vascular diseases, review of some of recent literature, with critical review of surgical treatment, 707
- Vasomotor System See Arteries, Blood vessels, Capillaries
- Veins See also Blood vessels, Embolism Thrombophlebitis, Thrombosis, Vena Cava
 - review of recent literature, 735
- Vena Cava, primary tumor of inferior vena cava, with clinical features suggestive of Chiari's disease, 50
- Veneral Diseases See also Gonorrhea, Syphilis
 - control in United States, 1133
 - public interest in 1135

- Venous Pressure** See Blood pressure
- Viruses** diseases caused by filtrable viruses, 506
- Vitamins** See also Diet and Dietetics
- A, gastric emptying time of dogs under conditions of vitamin A deficiency, 905
 - A measurement of vitamin A status of young adults by dark adaptation technic, 661
 - B influence of thiamine on blood sugar levels in diabetic patients 1079
 - B observations on induced thiamine (vitamin B₁) deficiency in man 785
 - B therapy, evaluation for diabetes, 679
 - C, purpura haemorrhagica due to arsphenamines, sensitivity in patients as influenced by vitamin C therapy, 319
- Volk, M. C.** Studies of blood in congestive heart failure with reference to reticulocytosis, erythrocyte fragility, bilirubinemia, urobilinogen excretion and changes in blood volume, 1230
- Waller, I. V.** Studies of blood in congestive heart failure with reference to reticulocytosis, erythrocyte fragility, bilirubinemia, urobilinogen excretion and changes in blood volume, 1230
- Watson, C. I.** Primary tumor of inferior vena cava, with clinical features suggestive of Chiari's disease 50
- Wayburn, I.** Relation between multiple peripheral neuropathy and cirrhosis of liver, 161
- Weber, I. C., Jr.** Protamine zinc insulin clinical study, report of group of diabetic patients in whose cases glycosuria was disregarded for 1 year, 670
- Wechsler, I. S.** Cerebral abscess (paradoxical) accompanying congenital heart disease, report of 2 cases 1282
- Wilder, R. M.** Observations on induced thiamine (vitamin B₁) deficiency in man, 785
- Williams, R. D.** Observations on induced thiamine (vitamin B₁) deficiency in man, 785

